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GYNÆCOMASTIA

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With a Foreword by

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FOREWORD

So far as I am aware this is the only book or monograph that has ever been written on gynæcomastia, and this is surprising for it is a condition which often "*stumps*" *the clinician* There is for instance considerable disagreement between pædiatricians, endocrinologists, physicians and surgeons concerning the management of puberty gynæcomastia Will it disappear spontaneously; how embarrassing is it to the adolescent boy, how neatly can the surgeon deal with it? The association between gynæcomastia and Klinefelter's syndrome is of considerable interest, for hyperplasia of the Leydig cells is a characteristic feature Is the gynæcomastia due to œstrogen and is the œstrogen produced by these cells? Perhaps it is in the adult, however, that gynæcomastia is especially puzzling So often it is difficult to explain the cause and to predict the prognosis It is in this type of case that even the experienced physician flounders and finds himself tempted to give serious consideration to such rarities as feminizing adrenocortical tumours

Dr Hall has made a valuable contribution by putting this puzzling physical sign *in its true perspective* *His extensive testicular biopsy studies have emphasized* the frequency with which gynæcomastia is accompanied by the "Klinefelter" picture of interstitial-cell hyperplasia and tubular hyalinization

I had the proud privilege of watching this book grow For some time I had regarded gynæcomastia as an endocrine enigma and I challenged Dr Hall to make a contribution to its solution He chose the subject for his M D Thesis and I was well aware of the high standard required for the Sydney M D I have been intimately concerned with the preparation of many M D Theses, including my own but I have never seen a project tackled so thoroughly He was not content only to read the literature He established personal contact with many of its principal authors No doubt, as time goes on, the problem of gynæcomastia will be completely solved, but when it is I believe this book will be regarded as one of the major contributions to that solution

P M F Bishop, D.M., F.R.C.P.

June, 1959

To PROFESSOR LORIMER DODS

whose stimulating influence was felt during the preparation of this book

CHAPTER I

DEFINITION

A great deal of confusion exists in the literature dealing with gynæcomastia; much of this can be attributed to the want of a satisfactory definition of the condition. Some writers have used definitions which refer to the external form of the breast, e.g.,

> Gynæcomastia may be defined as an affection of the male breast in which the gland tends to assume the size, shape and sometimes the functions of the female breast. (Cheatle and Cutler[1])

Apart from the objection that the secretion which may sometimes be expressed from the nipple in cases of gynæcomastia has never been shown to possess the chemical and physiological properties of milk, this definition confuses the appearance of an organ (the breast) with the state of a gland (the mammary gland).

Stieda,[2] as early as 1805, claimed that the etymology of the word gynæcomastia only permitted its use to describe the external form and volume of the breast, and, furthermore, that the histology of the breast in cases of gynæcomastia differed considerably from that of the functional breasts of women.

On the other hand, Karsner[3] has recently proposed an extended definition of the word gynæcomastia, in which he includes a detailed description of the usual histological changes seen in the condition.

> Gynæcomastia is an enlargement of the mammary gland or glands of males due to proliferation of connective tissue, dense in the general stroma and often loosely arranged in periductal regions, together with variable degrees of multiplication, elongation or branching of ducts or of all three, without formation of acini, accompanied by periductal or more widespread infiltration of lymphocytes, plasma cells, large mononuclear cells and occasionally eosinophil or neutrophil polymorphonuclear cells or both; secretion is frequently present in ducts, may be discharged spontaneously or manually expressed, but rarely if ever is it true colostrum or milk. This definition excludes pseudogynæcomastia due to the deposition of fat in the mammary region as well as suppurative or other essentially inflammatory processes, granulomatous lesions and neoplasms, either benign or malignant.

The principal objections to this definition are that it is very cumbersome and that it can only be used after histological study of the breast. The same objections apply to the most recent definition of gynæcomastia, namely that of Wheeler and his colleagues.[4]

Webster[5] has suggested a much simpler definition: "Gynæcomastia is a term applied to enlargement of the breast in males."

The Concise Oxford Dictionary defines the word breast as "the milk-secreting organ in women or the corresponding rudiment in men." This allows one to speak of "a breast" in normal men, implying the existence of a rudimentary organ and not merely denoting an area of the body as in the purely literary use of this word. Enlargement of such an organ could be judged in three ways: (i) By comparison with the opposite breast where the condition is unilateral, (ii) by comparison with the previous dimensions of the breast, and (iii) by comparison with the breasts of normal men.

However, one is generally concerned with enlargement of the glandular component of the male breast, as distinct from the deposition of fat in the breast or the occurrence of neoplastic and inflammatory swellings. This objection could be eliminated by speaking of true and false gynæcomastia. Alternatively, the word gynæcomastia could be reserved for enlargement of the glandular tissue. The following definition is therefore suggested: Gynæcomastia is a term applied to enlargement of the breast in males due to increase in the glandular component of the organ.

PREFACE

This book was written on the basis of a thesis prepared at Guy's Hospital between 1952 and 1955. The patients whose clinical histories form the subject matter of the text belong to two series, 85 men were studied at Guy's Hospital and a second series of 25 patients have been examined at Sydney Hospital. I am greatly indebted to the numerous physicians and surgeons who have so generously provided clinical and laboratory data concerning their patients and, in some cases, histological preparations. Special thanks are due to Dr Fuller Albright, who provided extensive data concerning two patients, to Dr W O Nelson, whose assistance in the interpretation of some of the more difficult testicular biopsies and whose generous encouragement have proved invaluable, and to Dr Charles W Charny, of Philadelphia, who very kindly provided a series of testicular biopsies of normal boys, without which it would have been impossible to discuss the microscopic appearance of the testis in adolescent patients. Dr Gordon Thomas, of Guy's Hospital, was entirely responsible for the photomicrographs, and for this exacting and time-consuming labour I wish to express my warmest thanks. The Departments of Medical Illustration at Guy's Hospital and Sydney Hospital have kindly provided photographs of patients and biopsies. Dr R A Melick has read the text in its various stages and has provided stimulating criticism, which I gratefully acknowledge.

Without the encouragement and assistance of Dr P M F Bishop this book would never have been written, and for his guidance and inspiration I am sincerely grateful. My task has been facilitated throughout by the loyal and friendly support of the publishers.

Peter F Hall

Macquarie Street,
Sydney,
October, 1958

CHAPTER II

HISTORY

Gynæcomastia, when well developed, is such an arresting phenomenon that it not only excites medical interest but arouses the curiosity of the layman. Reference is made to the condition in numerous myths and folk lores, in which it is often regarded as a punishment sent by the gods. Herodotus,[1] who lived during the fifth and sixth centuries B.C., gave one of the first descriptions of gynæcomastia, a condition which he encountered among the Scythians, who were considered an effeminate race. Hippocrates[2] mentions gynæcomastia among the same race, but he regarded the condition as a disease of equitation, resulting from excessive horse riding. In support of this view he pointed to the absence of gynæcomastia among the lower classes, who were too poor to buy horses.

Aristotle[3] mentioned gynæcomastia in his history of animals. He described the secretion of "milk" which could be expressed from the breast and claimed to have seen several cases himself. He further stated that when the priests enquired of the God of Lemnos as to the significance of gynæcomastia, they learnt that it was an ominous sign.[3, 4] The teachings of Aristotle were widely disseminated until the time of Galen, who invented the word gynæcomastia, which he defined as "an unnatural increase in the constituent fat of the breasts of men." Galen[5, 6] also wrote about enlargement of the glandular part of the male breast, a condition which he did not call gynæcomastia. He attributed a far-reaching significance to such enlargement.

It was an orthodox belief among the ancients that both sexes had "seed", but Galen was the first to suggest that the seed was the same in the two sexes, being expelled in men and retained in women. He regarded gynæcomastia* as being the result of retention of feminizing seed. He appears to have seen gynæcomastia associated with hypogonadism and failure of ejaculation. These views of Galen concerning sex differentiation remained in the literature for centuries.

The first surviving clinical description of gynæcomastia was that of Paulus Ægineta,[7] the last great Byzantine physician, who lived at the end of the sixth and beginning of the seventh century A.D.

> As at the season of puberty the breasts of females swell up, so in like manner those of males also swell to a certain extent; but for the most part they subside again. But in some cases, however, having acquired a beginning, they go on increasing owing to the formation of fat below.

This description of the normal breast development of boys at puberty was overlooked until recent years, when it became apparent that some degree of transient breast development is part of a normal male puberty (Chapter VII). Ægineta goes on to advise surgical treatment in those patients in whom the condition persists: "Wherefore as this deformity has the reproach of effeminacy it is proper to operate upon it." He gives a beautiful and concise description of the operation.

The remarks of Paulus Ægineta passed almost word for word into the writings of Arabic and Moorish authors whose works were read throughout Europe during the Middle Ages.

* The word gynæcomastia is here used as defined in this book, not as defined by Galen.

Sometimes enlargement due to the deposition of fat is difficult to distinguish from gynæcomastia Genera[illegible] even in the presence of fat [illegible] in this way, include pain and [illegible] of the areolæ When secret[illegible] glandular enlargement is present Finally, when fat is deposited in the region of the breasts, it is usually [illegible] which requires treatment by restriction of food [illegible] been lost, the glandular component of the breas[illegible] Occasionally this form of treatment is a necessar[illegible]

This definition is short and simple and avoids all controversial issues In addition it enables the term gynæcomastia to be used after a simple clinical examination At the same time it does not prevent pathologists from using the term, especially since the morbid histology in cases of gynæcomastia is essentially the same, no matter what has caused the condition to develop (see page 22)

I[illegible] be di[illegible] this [illegible] clinically at Guy's Hospital, 27 were submitted to operation, and in every instance macroscopic and microscopic evidence of glandular hypertrophy was found Peters and his colleagues[5] also found a very high degree of accuracy in the diagnosis of cases of gynæcomastia as revealed by specimens removed at operation It would therefore seem that clinical examination is sufficiently accurate to justify the simple definition already given

Defined in this way, gynæcomastia is not a disease, but a symptom or sign, the causes of which vary from a transient manifestation of puberty to a major disturbance of the general health

The histological characteristics of gynæcomastia are discussed in a later chapter (page 22) Here it may be pointed out that the exhaustive studies of Menville[6] and Karsner[3] have done much to justify the simple definition to be used throughout this book, in so far as these authors have shown that certain histological features invariably accompany enlargement of the gland, while other features are less constant in their appearance It has never been shown, however, that a particular histological [illegible] e is therefore complicated

The words gynæcomastism, gynæcomasty and gynæcomazia (gynæcomasia) are sometimes used instead of gynæcomastia Gynæcomastism is occasionally seen in the American literature, and is an attempt to anglicize the Greek word, but it is not euphonious Gynæcomasty is seldom used, and is neither Greek nor English. Gynæcomazia is derived from the Greek word *mazos*, which is confined to the Ionic dialect, and is therefore not suited to the medical vocabulary It is not true, as some have said, that mazos refers to the male breast and mastos to the female (Liddell and Scott[7]) Gynæcomastia is clearly, therefore, the word of choice, since it is both correct and orthodox

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CHAPTER III

RELEVANT LITERATURE

Since 1930, a number of papers have appeared on the subject of gynæcomastia These contributions form the basis of present-day knowledge of the subject and are therefore separated from the works of purely historical interest reviewed in the last chapter These papers deal with the subject as a whole, as opposed to a number of papers to be reviewed in later chapters which treat only special aspects of gynæcomastia

In 1930 Kriss[1] published an important paper on the subject of gynæcomastia; he gave an exhaustive review of the previous literature from which he gathered information concerning 269 examples of the condition Kriss stressed the importance of distinguishing gynæcomastia from enlargement of the breast due to the accumulation of fat and to the presence of tumours and also from what he called "mastitis adolescentium" In order to exclude these conditions by definition, Kriss defined gynæcomastia in the following terms

> An enlargement of one or both male breasts occurring at any age and brought about by hyperplasia of the glandular portion of the breast alone or hyperplasia of glandular and interstitial tissue combined

This definition formed a useful basis for the author's analysis of the cases taken from the literature This was the first paper to stress the importance of histological changes in the breast

In discussing the ætiology of gynæcomastia, Kriss began by considering such factors as sexual continence (taking us back to Galen's idea of retained seed), trauma and local pressure He then digressed into a discussion of the two theories of the determination of sex which were widely held at the time namely (i) the Herbst-Steinach theory, which attributed every aspect of sex (primary as well as secondary sexual characteristics) to the action of hormones, and (ii) Hallian's theory that sex is genetically determined

Kriss accepted the second theory which was hardly surprising because Hallian was his chief Kriss endeavoured to support Hallian's theory by his own views on the ætiology of gynæcomastia These observations are interesting in view of recent studies which point to disturbances in sex differentiation as a factor in the ætiology of certain types of gynæcomastia (page 98)

Kriss stated that castration of male animals did not produce breast development, and from this he concluded that the testes played no important part in the ætiology of gynæcomastia

In 1933 Menville[2] published a paper on gynæcomastia which summarized the literature up to that year The chief value of Menville's paper lies in its splendid account of the histology of the breast in gynæcomastia The author showed that increase in stroma as well as in parenchyma was seen in all cases of gynæcomastia Menville showed that the histological changes seen in gynæcomastia resemble those of fibroadenoma of the female breast He further pointed out that there was no virtue in describing fibroadenoma of the male breast which he showed was merely a further extension of the usual changes found in gynæcomastia and was seen in long-standing cases By his thorough and scientific approach to the histology of the breast in gynæcomastia, Menville cut short the use of numerous terms and classifications which threatened to reduce the subject to a state of confusion

During and after the Renaissance, gynæcomastia received the passing mention afforded to a medical curiosity. For example, in 1669 Charleton[12] described an interesting case of gynæcomastia with secretion from the nipples:

> *Vidi enim Januse Antonin Benzum ex oppido Portus Mauricii, annum agentem XXXii; pallidum barba rara, pingui habitu e cuius mamilli lactis tantum profluebat, ut infantim fermi lactari potuisset, ne solum effluebat, sed impulsu ferebatur Miles diu erat, et non lenia tota vita passus incommoda* *

... 1694, used gynæcomastia ... was due to the expression ... e puerperium

During the next 150 years little appears to have been written on the subject of gynæcomastia *For example, a book on diseases of the breast, written by Velpeau,*[13] appeared in Paris in 1854, during the last half of the nineteenth century this became a standard textbook on the subject Velpeau does not mention the word gynæcomastia and devotes only a few pages to diseases of the male breast. However, in 1848 von Basedow[8] mentioned gynæcomastia in describing the disease which bears his name He referred to the case of a man suffering from a severe degree of thyrotoxicosis who showed gynæcomastia, while women similarly affected showed atrophy of the breasts

In the first volumes of *Annals of Surgery*, Jonathan Hutcheson[9] published three papers reporting cases of gynæcomastia One patient was a boy whose mother suffered from acromegaly

In more recent times (1925) Corda[10] pointed out that testicular atrophy was seen in some cases of cirrhosis of the liver, and in the following year Silvestrini[11] drew attention to an observation he had first made in 1904, namely, that gynæcomastia is sometimes seen in patients suffering from cirrhosis of the liver The triad of cirrhosis, testicular atrophy and gynæcomastia is sometimes referred to as the Silvestrini-Corda syndrome Silvestrini was of the opinion that cirrhosis produced an "endocrine imbalance" which in turn caused gynæcomastia "*Perturbamento dell' equilibrio ormonico che mantiene i carrattice sessuale*"†

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* ... Mauricius in his 32nd year, ... much milk flowed forth that ... spurted out He had been a ... e whole of his life

† Disturbance of the hormonal balance which maintains ... development

relevant literature in the light of his own observations, citing relevant experimental evidence and suggesting a possible mechanism for each group of cases of gynæcomastia. However, this segregation of different groups of patients with gynæcomastia was not carried to the fullest possible extent, and the author sometimes discusses gynæcomastia as a whole when it would have been more appropriate to deal with the condition from an ætiological point of view. For example, Karsner studied the age incidence of gynæcomastia by decades, although it would be preferable to separate (for example) those cases associated with liver disease from those associated with puberty Today more is known about the causative diseases concerned, and it is usual to consider gynæcomastia according to the associated ætiological factors.

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Menville also gave a careful review of the occurrence of gynæcomastia during the course of a number of endocrine diseases. After a study of all the recorded examples of gynæcomastia associated with testicular lesions, he concluded that any disturbance of the "endocrine system" could produce gynæcomastia. Unlike Kriss, Menville saw the importance of testicular lesions in the ætiology of gynæcomastia. Beyond this, however, Menville's conception of the ætiology of the condition was lost in speculation on the subject of sex differentiation. He believed that sex differentiation was the result of a balance between male and female factors, and that important causes of gynæcomastia included bisexuality and a lack of "male sexual influence".

It is of course true that sex differentiation is the result of competition between male and female influences, but Menville was not in a position to understand the possible role of these influences in the ætiology of gynæcomastia. He failed to state clearly that gynæcomastia can affect young men in whom no other evidence of "lack of male sexual influence" exists. Moreover, Menville was not to know that synthetic œstrogens were soon to be widely used in medicine and that gynæcomastia could be induced in normal men by these hormones, the breast showing histological appearances identical with those which he described so carefully as typical of gynæcomastia.

Karsner[3] reviewed the literature dealing with gynæcomastia before 1946. In this paper we encounter clinical endocrinology as we know it today. The author found that unilateral gynæcomastia was more common than bilateral, and that the left and right breasts were affected with almost equal frequency. The third decade provided most of his 280 cases, and the majority of patients described a gradual increase in the size of the breasts during a period of several weeks and thereafter no change. One case in ten gave a history of trauma, although this was sometimes as long as three years before the onset of gynæcomastia.

Karsner gave an excellent account of the histology of the breast in gynæcomastia; he distinguished between the stroma of collagenous tissue and the periductal connective tissue, a distinction which he stated was not possible in the normal male breast. The stroma shows great hypertrophy in gynæcomastia, with fibroblasts and inflammatory cells, the whole tissue being loosely arranged as the result of œdema.

In discussing the ætiology of gynæcomastia, Karsner made it clear that the histological changes in the breast were not related to the causal factors involved. In other words, the morbid anatomy is essentially the same, no matter under what circumstances the gynæcomastia appears. He favoured excessive secretion of œstrogen as the fundamental cause of gynæcomastia and stated that both breasts were usually enlarged when the condition resulted from some manifest endocrine disease, although there is often some inequality in the size of the two breasts. Karsner believed that trauma is either coincidental or merely serves to draw attention to an existing swelling of the breast, but does not cause gynæcomastia.

In addition to these clinical and histological observations Karsner made free use of the methods of hormone assay in current use at the time:

> Throughout the following discussion emphasis is laid on the importance of assay of hormones or their products. This is with full recognition of the sources of error and the fact that such assays do not necessarily indicate what happens to the hormones in the body. Yet these assays are the nearest objective approach to the problem.

This statement gives some indication of the progress made by endocrinology in the thirteen years which separate the papers of Menville and Karsner. Consistent with this enlightened attitude Karsner remains cautious in applying animal experiments to man. For example he was able to see that, although androgens cause proliferation of the mammary glands of experimental animals, there is little evidence to show that they have the same effect in man.

This approach to the problem enabled Karsner to see that gynæcomastia arose from a number of different causes, and these he dealt with in turn, reviewing the

relevant literature in the light of his own observations, citing relevant experimental evidence and suggesting a possible mechanism for each group of cases of gynæcomastia. However, this segregation of different groups of patients with gynæcomastia was not carried to the fullest possible extent, and the author sometimes discusses gynæcomastia as a whole when it would have been more appropriate to deal with the condition from an ætiological point of view. For example, Karsner studied the age incidence of gynæcomastia by decades, although it would be preferable to separate (for example) those cases associated with liver disease from those associated with puberty. Today more is known about the causative diseases concerned, and it is usual to consider gynæcomastia *according to the associated ætiological factors*.

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CHAPTER IV

CLINICAL AND LABORATORY METHODS IN GYNÆCOMASTIA

CLINICAL METHODS

HISTORY

It goes without saying that a thorough history is the first requirement for the investigation of a patient suffering from gynæcomastia In particular, certain points deserve special emphasis.

Gynæcomastia.—The onset and evolution of breast development, together with the presence or absence of pain and secretion, are important

Puberty.—The age of onset of puberty and the timing of the individual events which go to make up puberty are of special interest (i e, age at which pubic and axillary hair appeared, shaving first became necessary, breaking of the voice, erections and emissions first occurred, etc)

Sexual Function.—It is necessary to obtain some measure of sexual function following the onset of puberty, e g libido, erections, emissions and fertility

Past Health.—Some clue to the cause of gynæcomastia can occasionally be found in the previous medical history. The following conditions are especially relevant

(1) Jaundice and liver disease
(2) Mumps
(3) Traumatic lesions of the breasts or testes
(4) Addison's disease
(5) Thyrotoxicosis
(6) Prostatectomy
(7) Tuberculosis
(8) Syphilis
(9) Leprosy
(10) The use of or exposure to the following drugs (i) œstrogens, (ii) androgens, (iii) chorionic gonadotrophin, (iv) deoxycorticosterone or adrenocortical extract, (v) digitalis, (vi) deep-ray therapy, (vii) radioactive isotopes, (viii) liver poisons
(11) Undescended testes
(12) Malnutrition

Family History.—Gynæcomastia sometimes appears to run in families

PHYSICAL EXAMINATION

In addition to the usual physical examination, certain points are especially important

Breasts

Appearance.—The size shape and symmetry of the breasts are recorded

Nipples.—The size, shape, symmetry and presence of pigmentation are noted

Glandular Tissue.—The presence, extent and tenderness of glandular tissue as well as evidence of extraneous lumps are important

Fat.—The amount and distribution of body fat in general and the presence of fat in the vicinity of the breasts in particular should be recorded

Secretion.—An attempt can be made to express secretion from the breast by gentle manipulation

The size of the breasts is important for purposes of subsequent comparison. Most attempts to measure the chest wall have proved fruitless so far as providing a record of the size of the breasts is concerned (especially in dealing with growing boys).

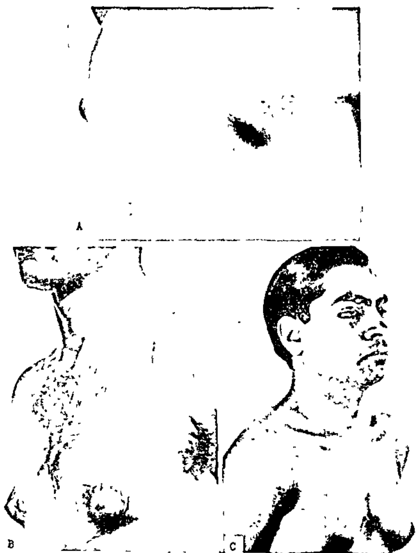


FIGURE 1

female breast

A rough measure of the extent of gynæcomastia in a given individual can be obtained by means of a photograph An oblique view of the chest is taken, and this will serve for the purpose of comparison with subsequent photographs to indicate changes in

the severity of the condition (Figure 1) Enlargement of the breasts which is quite obvious on clinical examination but which is scarcely evident in an oblique view of the chest is described as being of Grade I severity Grade III includes patients whose breasts are comparable in size with those of adolescent girls Grade II severity refers to those breasts which are obviously enlarged in a photograph of an oblique view of the chest but which fail to reach the size of those of Grade III (Figure 1). This classification is necessarily very crude, but it gives some measure by means of which one patient can be compared with another.

The examination of the breast should be conducted with the patient first lying down, then standing Palpation is best performed against the contracted pectoral muscle by asking the patient to put his hands on his hips. The breasts should be handled *gently because they are frequently tender. Occasionally lymph glands* can be palpated in the axilla in patients suffering from gynæcomastia

The most important disease of the male breast to be distinguished from gynæcomastia is carcinoma Usually this distinction is possible on clinical examination

sometimes encountered,
suggestive of malignant
concentric in relation to
of cases

Body Measurements

The height and weight of patients should be measured; the height enables the rate of growth of adolescents to be estimated and by comparison with the span assists in defining eunuchoidism (page 18) The span is measured from the tip of one middle finger to that of the other, with both arms outstretched. The upper segment of the body (U S) is measured from vertex to pubic symphysis, and the lower segment (L S) from the symphy is to the floor When the span exceeds the height by more than two inches, and when the lower segment (L S) exceeds the upper (U S) by more than one inch in patients over the age of 14 years, in the absence of arachnodactyly, the stature may be described as eunuchoid This conclusion can be checked by reference to tables in which span, U S and L S measurements are given for various heights, weights and ages [1]

Genital Organs

The genital organs are examined in the usual way Unfortunately, measurements

Secondary Sexual Characteristics

Secondary sexual characteristics can be examined and conveniently recorded as follows

(*a*) Hair —(i) Head temporal recession of the hair-line and baldness (ii) Face *some estimate of the frequency of shaving and* the distribution and texture of facial hair (iii) Pubes amount and distribution (iv) Axilla amount and distribution (v) Body hair amount and distribution (vi) Limb hair amount and distribution

(*b*) Voice *Broken or unbroken*

(*c*) Prostate A rough estimate of the size of the prostate gland can be made by comparison with the size of the normal adult gland

Special Investigations

Hormone Assays

(*a*) *17-Ketosteroid Estimation*.—Throughout this book estimation of 17-ketosteroid excretion refers to t[illegible]
adult men of 4 to 20 mg [illegible]
from the figures of Robins[illegible]

(*b*) *Urinary Gonadotrophins*.—Urinary gonadotrophins were measured by the method of Klinefelter, Albright and Griswold,[6] using immature female mice and expressing the result in mouse units. In a series of 100 normal men whose urinary gonadotrophins were studied at Guy's Hospital, the values fell within the normal range of >6<32 mouse units.

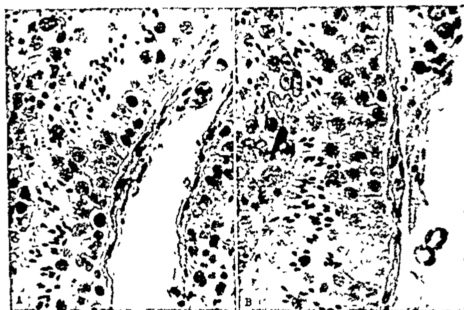


Figure 2

The normal adult male testis. A specimen obtained by means of biopsy from a man, aged 33 years, who complained of psychogenic impotence. (A) Shows normal spermatogenesis. Meiotic figures are seen in spermatocytes and Sertoli cells are seen between the germinal cells. (B) Shows spermatogenesis and a nest of Leydig cells.

(*c*) *Urinary Œstrogens*.—Unless otherwise stated, urinary œstrogens were measured by a chemical method performed at University College Hospital under the direction of Dr. G. I. M. Swyer. The method (a modification of that described by Brown) is described in detail by Braunsberg and her colleagues.[7, 8, 9, 10, 11] The range for normal males is discussed in Chapter VII.

Examination of Semen

The chief interest in the examination of semen in cases of gynæcomastia lies in the detection of azoospermia in Klinefelter's syndrome and prepubertal testicular failure. The volume of the ejaculate and the number of sperms per millilitre are given, and the motility is graded from 0 to 4 (4 means that more than 80% of sperms are motile).

Testicular Biopsy

The most satisfactory method of testicular biopsy is that described by Simmons[12] and by Charny[13] The most important precaution is to avoid the epididymis, which in most cases is not difficult if its presence is kept in mind. The histology of the tubules and their contents is of particular importance in patients suffering from gynæcomastia Some quantitative estimation of the amount of Leydig cell tissue

method relates the number of Leydig cells to the number of tubules and is based upon counts of the number of these cells related to 100 tubules * The method is easily mastered, and counts performed on one biopsy by different observers are in close agreement. It remains, however, to establish the relationship between the number of Leydig cells and their functional capacity.

DEFINITIONS

The three words hypogonadism, infantilism and eunuchoidism are loosely applied in the literature of endocrinology at the present time, and different authors use these words to denote different entities Throughout this book these words are defined in the following terms

Hypogonadism may be defined as a condition of failure, partial or complete, of the endocrine or germinal functions of the gonads, or failure of both This definition implies that the failure is bilateral In the male, hypogonadism is sometimes referred to as testicular failure

The word infantilism, unqualified, is not used in this book, and sexual infantilism is defined as the persistence of the prepubertal condition of the genital organs (other than the gonads) and the failure of development of secondary sexual characteristics in adults. An adult will be defined for this purpose as an individual over the age of 18 years It should be noticed that sexual infantilism defined in this way takes no account of stature The state of the gonads is excluded from the definition, because in cases of sexual infantilism this may not be that of the normal prepubertal gonad

Eunuchoidism may be defined as a bodily configuration in which, after the age of 14 years, the span exceeds the height by more than two inches and/or the lower segment exceeds the upper by more than one inch The terms "span" and "upper segment" have been defined above (page 16) This definition does not take into

It may be argued that the word

gin of the word bears little relation

the term is frequently applied to

genital organs will either greatly

restrict the use (and hence the value) of the word or will preclude exact definition The term eunuchoidism or eunuchoid stature is a useful way of referring to the physique of individuals in whom growth of the limbs is excessive because it has continued beyond the stage at which the epiphyses fuse in normal individuals This can occur in hypogonadism of gonadal or of pituitary origin Sometimes such a stature is encountered in individuals with no endocrine abnormalities, e g in cases of arachnodactyly. Here the context will indicate the nature of the condition

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* The count is expressed as the number of Leydig cells per tubule

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CHAPTER V

THE MALE BREAST

ANATOMY

Except in obese subjects, the male breast is so poorly developed as to remain invisible to inspection of the chest wall, and the only evidence of glandular tissue consists of a few minute nodules which can be felt as irregularities by the examining fingers as the areola is moved across the chest wall When masses of fat cause the loose subcutaneous tissue of the chest wall to fill out in imitation of the female breast, no glandular tissue can be felt beyond the margin of the areola This accumulation of fat is usually seen in the presence of well-marked generalized obesity and is seldom a purely local phenomenon

When the glandular component of the male breast does enlarge, it is separated from the overlying skin (except in the region of the areola) by a layer of adipose *tissue, as in the female. The* mammary tissue, however, is not encapsulated, and some of this can be felt directly beneath the skin Even in the presence of considerable amounts of fat it is generally possible to feel the glandular component of the breast when this is enlarged

EMBRYOLOGY

[illegible]

Between the third and fourth months, the basal cells surrounding the primitive nipple form a series *of down-growing sprouts, which gradually invade the underlying* tissue and are canalized to form milk channels

In the final stage of embryonic mammary development, the milk ducts form a series of branching channels with a definite lumen lined by two or three layers of cells The nipple gradually everts as the result of subepidermal connective tissue proliferation The lobular buds, from which clusters of alveoli form (in the female) after sexual maturity, do not develop until puberty [1, 2]

After birth, epithelial activity continues for a few weeks, and then in the male [illegible] According to Fabris[3] glandular tissue between [illegible] newborn, [illegible] he third [illegible] *eath the* nipple, together with some secretion, is said to occur in 10% of infants. At this [illegible]

[illegible] epithelium with desquamation of lining cells occurs The lumen of the ducts becomes closed, and the periductal connective tissue is seen to be hyalinized These changes are seen in normal infants of either sex

PUBERTY

At the time of puberty about 70% of boys show a palpable button-like node, the "puberty node", beneath the nipple Jung and Shafton[4] refer to this structure as the "subareolar node" The terms "puberty mastitis" and "adolescent mastitis" imply something more than physiological activity, and are therefore less desirable

This awakening of the male breast is seen under the microscope to produce changes like those found after birth The tubules dilate and increase in length, and [illegible] The periductal tissue becomes more vascular, [illegible] the ends of the terminal tubules [illegible] the alveoli which later develop in the female

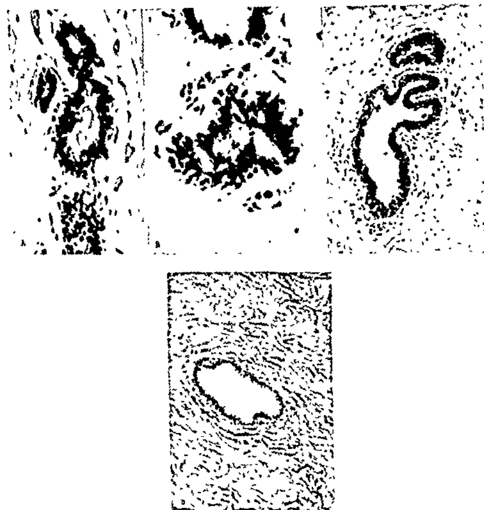


FIGURE 3
(A) Essential gynæcomastia (B) Prepubertal testicular failure (C) Klinefelter's syndrome

Between the ages of 16 and 17 years, involutional changes occur which involve collapse of the tubules, condensation of connective tissue and a diminution in size of the epithelial cells The male breast has now run its full life span, and gradually sclerosis of the stroma, with obliteration of the ducts and vessels, sets in.[2]

THE BREAST IN GYNÆCOMASTIA

The breast in cases of gynæcomastia shows histological evidence of stimulation and closely resembles the mammary tissue of girls at the time of puberty.

MACROSCOPIC

When the breast is removed at operation in cases of gynæcomastia, it resembles the female breast at puberty in its gross appearance Sometimes it has a firm, discrete, nodular character, which some observers have called fibroadenoma, on the grounds that in certain cases the tissue is encapsulated [5] This encapsulated form of the male breast is seen in those patients in whom gynæcomastia has been of long duration and calls for no special terminology, the use of the term fibroadenoma in this context is misleading and superfluous

MICROSCOPIC

Briefly, the picture is one of growth of mammary ducts and of periductal stroma, but lobule formation is absent Proliferation of duct epithelium occurs together with some desquamation of cells into the lumen Small projections of epithelium into the lumen may occur, and in some instances the ducts are dilated and full of secretion [2, 6, 7]

Around the ducts there is an increase in connective tissue, infiltrated by wandering cells Sometimes the subcutaneous sweat glands undergo hypertrophy The picture is often indistinguishable from the early development of the normal female breast at puberty [2, 5, 6] Mitoses are sometimes seen in the periductal connective tissue cells, and lymphocytic and plasma cell infiltration with a few eosinophil cells may occur in this tissue

Menville[5] has followed the changes in the microscopic features of gynæcomastia in long-standing cases After one year changes are seen which resemble fibroadenomatous hypertrophy in women Menville produced convincing evidence that this appearance is a further extension of hyperplasia and not a separate pathological entity

guishes the stroma from the periductal connective tissue The stroma of gynæcomastia differs from that of the normal male breast only in amount The periductal tissue, *however, is loosely arranged and is infiltrated with lymphocytes, plasma cells* and mononuclear cells This distinction is not possible in the normal male breast

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he duct or its branched
that the myoepithelial
lie within the
are stimulated
mastia may be
so extensive that they push their way into the lumina of the ducts

All observers seem to agre
female breast do not appear
namely, neonatal gynæcomasti
produce considerable quantities of " witches milk " secretion
mean that alveoli are present, because gynæcomastia occurring at *puberty* may be associated with some secretion, but acini are not to be found histologically [8] So far there have been few reports of the microscopic appearance of the breast in neonatal *gynæcomastia*, but in general they are said to resemble miniature lactating glands [8]

Although differences in microscopic features are noticed between one case and another, and even within one specimen, these differences are of minor importance. As yet there is no evidence to show that histological differences are consistently associated with different causal factors. Furthermore, elaborate classifications of histological features of the breast in gynæcomastia have not increased our understanding of the ætiology or pathogenesis of the condition and are best avoided, because they are tedious and confusing. In the pages which follow, reference will be made to the typical microscopic appearance of the breast in gynæcomastia. This should be taken to mean that the changes already described are present—i e. (*a*) increase in length and branching of ducts ; (*b*) epithelial hyperplasia ; (*c*) increase in stroma and in periductal connective tissue ; and (*d*) invasion of the stroma by inflammatory cells.

These figures serve to emphasize the fact that the appearances are not specific for any one type of gynæcomastia

THE ACTION OF HORMONES ON THE BREAST

Until more is known of the endocrine control of mammary function in man under normal conditions, our knowledge of this subject will be based upon conclusions drawn from experiments in which individual hormones are administered to animals and the response of the breast is studied. Some of these experiments are relevant to the ætiology of gynæcomastia.

ŒSTROGENS

The action of œstrogens upon the breast varies from species to species. The chief difference lies in the capacity of these hormones to induce alveolar development Three types of response to œstrogens are encountered in animals[9, 10, 11]. (i) that in

(dog)

Man appears to belong to the first group, although detailed studies have not been undertaken

(*c*) Periductal connective tissue increases, becomes more vascular, and is invaded by lymphocytes and polymorphonuclear cells (*d*) Lobule formation does not occur, although sometimes the ends of the ducts become dilated, forming the so-called lobule buds

These changes are reflected by an increase in the overall size of the breasts.

The breasts may be stimulated in this way both in man and animals by natural and synthetic œstrogens, which appear to produce the same effects both by local inunction and by oral administration. In the case of locally applied ointments one breast alone is affected, unless the ointment is very strong and is applied frequently, in which case both breasts enlarge—presumably because sufficient hormone has been absorbed into the bloodstream to affect the other breast[12]

In certain species very large doses of œstrogen appear to stimulate the development of alveoli It is generally believed that alveoli in the breasts of women do not owe their formation to œstrogens

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tissue cells, and lymphocytic and plasma cell infiltration with a few eosinophil cells may occur in this tissue.

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Karsner[6] pointed out that too little attention is generally given to the alterations of the stroma In fact, the enlargeme [illegible] to proliferation of connective tissue , [illegible] as a rule, contribute very much to th [illegible] guishes the stroma from the periductal connective tissue The stroma of gynæcomastia differs from that of the normal male breast only in amount The periductal tissue, however, is loosely arranged and is infiltrated with lymphocytes, plasma cells and mononuclear cells This distinction is not possible in the normal male breast

Epithelial hyperplasia leads to an increase in the number of layers of cells lining the ducts up to five or six deep Budding of the ducts is sometimes seen—either as narrow branching structures or as spherical projections from the duct or its branched prolongations (Figure 3) Karnauchow[44] has recently shown that the myoepithelial [illegible] lie within the [illegible] are stimulated [illegible] mastia may be so extensive that they push their way into the lumina of the ducts

All observers seem to agre [illegible] the female breast do not appear [illegible] n— [illegible] may [illegible] witches milk [illegible] trily [illegible] cause gynæcomastia occurring at puberty may be associated with some secretion, but acini are not to be found histologically [8] So far there have been few reports of the microscopic appearance of the breast in neonatal gynæcomastia, but in general they are said to resemble miniature lactating glands [8]

in the presence of œstrone. Androsterone does not cause mammary growth in mice, but *17-methyl testosterone* causes alveolar development in this species and duct growth in the male guinea-pig.[1]

Enough has been said to indicate that differences in the response of the breast to androgens, as between one species and another and between one androgen and another, are so great that no simple general statement can be made The importance of this point lies in the fact that gynæcomastia has sometimes been attributed to the action of androgens However, in the monkey, the animal whose breast tissue is thought most closely to resemble that of man, stimulation of the ducts does not occur, but instead a characteristic heaping up of duct epithelium is seen,[1] and this change is not found in the breast in cases of gynæcomastia [5, 6]

HORMONES OF THE ADENOHYPOPHYSIS

Recent experimental data make it unnecessary to postulate the existence of mammoger

typical of

physectom

prolactin, ACTH and growth hormone [19, 20, 21] Changes in the relative doses of these hormones will produce lactation With these results obtained by using known hormones, it is tempting to envisage the control of mammary gland activity as proceeding without the aid of hypothetical hormones In these experiments ACTH is used to restore the physiology of the hypophysectomized animal to normal, but growth hormone appears to exert some specific effect upon breast development. It is true that the purity of present-day preparations of prolactin, ACTH and growth hormone may be suspect However, these hormones conform to certain chemical

The mammary growth-promoting actions of œstrogen and progesterone are abolished by hypophysectomy but restored by the concomitant administration of insulin [22] This observation accords well with the fact that growth hormone and

of œstrogens and progesterone from the ovary, and by way of prolactin, which stimulates the development of alveoli and promotes the function of lactation There is no evidence to suggest that prolactin plays an important part in the ætiology of gynæcomastia, and the significance of prolactin in the male is uncertain It is

of growth hormone in normal breast function awaits further elucidation

CHORIONIC GONADOTROPHIN

The action of chorionic gonadotrophin in men has been studied in detail by Maddock and Nelson [31] Nine men were treated by injection Of these, five complained of a decline in sexual potency which was not absolute, normal adult sexual development being present, two suffered from hypogonadotrophic hypogonadism (see page 46), one was a recent traumatic castrate, and one had Addison's disease

The effects seen in the five patients who complained of some decline in potency may be summarized as follows (i) increase in the urinary excretion of œstrogen, (ii) increase in 17-ketosteroid excretion, (iii) changes in testicular histology

It would seem that, in the absence of the pituitary gland, œstrogens either do not stimulate the breast or produce only a partial response In the presence of even minute remnants of anterior pituitary, however, œstrogens appear to produce their full effect [13, 14, 15, 16, 17] Malnutrition increases the threshold of œstrogenic stimulation of the breast.[18]

The changes produced by œstrogen are almost identical with those of gynæcomastia Gesc
men receiving
suffering fron
produced by
monkeys by the injection of 500 rat units of œstrin daily for ten days

Further support for the role of œstrogens in the ætiology of gynæcomastia has emerged from histochemical studies of the breast in this condition. Fisher and Creed[40] found abnormal quantities of hyaluronic acid in the stroma of enlarged male breasts. Ihnen and Perez-Tamayo[41] made similar observations in the case of fibroadenoma in the female, and it has been shown that the administration of œstrogens causes an increase in the content of hyaluronic acid in the connective tissue of those structures which are especially sensitive to œstrogens, e.g , the breast, the sexual skin of the monkey,[42] and the rooster's comb [43]

ANDROGENS

Under certain conditions androgens are capable of stimulating the breast Astwood and Geschickter[29] studied the effect of androgens upon the breast in rats and reported the following findings

1 Until the rat is six weeks old, breast development is identical in males and females, normal and castrate In fact, in each case the breast weight increases in proportion to the body weight

2 After the sixth week in females, increase occurs in length and diameter of the ducts Twigs develop along the course of the ducts Thereafter the breast undergoes cyclical changes The duct lumen increases and the twigs also enlarge during pro-œstrus and di-œstrus , after œstrus, regression takes place Pregnancy brings about the first appearance of lobules and alveoli

3 After the sixth week in males, dense clusters of alveoli are seen along the sides and around the ends of the ducts No further increase in size and number of ducts occurs

Œstrone will bring about the appearance of adult female breasts in sexually immature rats of either sex Testosterone will cause alveolar development but does not affect the length and size of the ducts—i e it produces the type of breast seen in the adult male, when injected into immature rats of either sex

There appears to be a considerable difference between the response shown by different species to androgens Van Wagenen and Folley,[30] using monkeys, found very little macroscopic duct development with testosterone but a characteristic heaping up of duct epithelium In man, no reports have appeared concerning the action of androgens upon the male breast, and the response seen in the monkey may not be the same as that seen in man. Klinefelter has reported the occurrence of gynæcomastia in a man during androgen therapy In a personal communication Dr Klinefelter stated that the histological appearance of the breasts, which were removed at operation, was essentially the same as that seen in other forms of gynæcomastia

Again, the conversion of androgens to œstrogens in the body is now an accepted metabolic reaction in man,[37, 38, 39] so that the action of androgens upon the breast may be complicated by conversion of these hormones to œstrogens Dehydroepiandrosterone causes duct growth in the mouse, but causes alveolar development

ectomized-ovariectomized animals were treated with hydrocortisone and œstrogen, or when ovariectomized animals were treated with ACTH and œstrogen. Selye believes that his results may help to explain the occasional example of the sudden onset of lactation following exposure to acute stress

THYROID

Evidence is lacking that thyroid hormone is necessary for the growth of the

CONCLUSION

It is apparent that much remains to be learnt about the action of hormones on the human breast It seems likely that œstrogens are responsible for duct development and for increase in stroma, while progesterone causes alveolar development, and prolactin supplies the further stimulation required for lactation As in

of androgenic activity So far it has not been possible to obtain such proof, and animal experiments make it seem probable that the microscopic changes seen in

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(*a*) evidence of Leydig cell stimulation, (*b*) signs of seminiferous tubule damage; (iv) gynæcomastia (in two cases).

Increase in œstrogen excretion began during the 24 hours following the first injection and reached levels of more than four times the amount excreted before treatment A rapid fall was noticed within the 24 hours following the last injection.

The 17-ketosteroid excretion also increased during the course of treatment, but varied considerably in relation to previous levels and in comparison with œstrogen excretion

The Leydig cells were smaller and darker than normal and increased in number. They showed more granules and more lipoid droplets, although the size of the latter was diminished. The tubules were small and showed necrosis of the germ cells, cessation of spermatogenesis and peritubular fibrosis The Sertoli cells appeared to be normal Sperm counts fell during treatment and returned to normal after injections were stopped In the two cases showing gynæcomastia, tenderness of the breasts was a feature, and the size of the swellings was between 3 and 5 cm in diameter

The two cases of hypogonadism showed a rise in 17-ketosteroid and œstrogen excretion The castrate showed no increase in the excretion of 17-ketosteroids or œstrogens, while the patient with Addison's disease showed a rise in the excretion of both 17-ketosteroids and œstrogens

These studies suggest that chorionic gonadotrophin affects the breasts indirectly [illegible] injections of [illegible] this hormone [illegible] ile histological [illegible] eroids suggest [illegible] of the patient [illegible] source of the [illegible] atients This paper provides the best evidence so far available in man that the Leydig cells represent the major source of testicular œstrogens Chorionic gonadotrophin exerts an effect upon the Leydig cells which resembles that of interstitial cell-stimulating hormone The importance of these observations will be seen in Chapter VIII, where it will be argued that gynæcomastia may result from excessive stimulation of the Leydig cells, which produce, as the result of this stimulation, excessive quantities of œstrogen

PROGESTERONE

Progesterone stimulates the formation of lobules and of alveoli in females after puberty, and in this way prepares the breast for its definitive role in lactation Progesterone probably plays no part in the behaviour of the normal male breast, and so far there is no evidence to incriminate this hormone in the production of gynæcomastia [2]

ADRENOCORTICAL HORMONES

Studies of breast development in adrenalectomized animals have so far failed to establish an essential role for the adrenal cortex in the normal development of mammary tissue Variable results have been reported from experiments involving the administration of cortical hormones Some workers report growth of ducts under the influence of [illegible] the monkey and in the *guinea-pig*, while othe[illegible] lings [1, 32, 33, 34] Deoxy-corticosterone exerts [illegible] n in promoting duct development in spayed [illegible] produces little effect [35]

Results with cortisone and hydrocortisone are frankly contradictory Some workers have described inhibition of duct growth by cortisone,[35] while Selye[36] reported considerable mammary gland stimulation with secretion when adrenal-

CHAPTER VI

THE CAUSES OF GYNÆCOMASTIA

It has already been stated
caused by a number of diseases.
those cases of gynæcomastia re
is available to establish the true nature of the underlying condition and its relationship to the gynæcomastia.

1. Gynæcomastia associated with physiological states
   - (a) Neonatal gynæcomastia.
   - (b) Essential gynæcomastia
   - (c) Involutional gynæcomastia

2. Gynæcomastia due to underlying disease.

   A Diseases of the endocrine glands

   I. Diseases of the testes.
   - (a) Prepubertal testicular failure
   - (b) Klinefelter's syndrome
   - (c) Leprosy
   - (d) Mumps
   - (e) Orchitis of unknown ætiology.
   - (f) Tumours: Teratoma
     Chorionepithelioma
     Seminoma
     Interstitial cell tumour
     Sertoli cell tumour.
   - (g) Radiation
   - (h) Undescended testes
   - (i) Castration
   - (j) Trauma
   - (k) Unilateral testicular lesions Varicocœle, atrophy of unknown ætiology

   II Diseases of the adrenal cortex
   - (a) Tumour
   - (b) Hyperplasia
   - (c) Stress

   III Diseases of the thyroid gland
   - (a) Hyperthyroidism
   - (b) Hypothyroidism

   IV Diseases of the pituitary gland
   - (a) Acromegaly
   - (b) Chromophobe adenoma
   - (c) Hypopituitarism

   V Disorders of sex.
   - (a) Hermaphroditism: True
     False.
   - (b) Transvestism

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CHAPTER VI

THE CAUSES OF GYNÆCOMASTIA

to the gynæcomastia.

1 Gynæcomastia associated with physiological states
- (a) Neonatal gynæcomastia
- (b) Essential gynæcomastia
- (c) Involutional gynæcomastia.

2 Gynæcomastia due to underlying disease

A Diseases of the endocrine glands

I. Diseases of the testes.
- (a) Prepubertal testicular failure
- (b) Klinefelter's syndrome
- (c) Leprosy
- (d) Mumps
- (e) Orchitis of unknown ætiology
- (f) Tumours: Teratoma, Chorionepithelioma, Seminoma, Interstitial cell tumour, Sertoli cell tumour
- (g) Radiation
- (h) Undescended testes
- (i) Castration
- (j) Trauma
- (k) Unilateral testicular lesions: Varicocœle, atrophy of unknown ætiology

II Diseases of the adrenal cortex.
- (a) Tumour
- (b) Hyperplasia
- (c) Stress

III Diseases of the thyroid gland.
- (a) Hyperthyroidism
- (b) Hypothyroidism

IV. Diseases of the pituitary gland
- (a) Acromegaly
- (b) Chromophobe adenoma
- (c) Hypopituitarism

V Disorders of sex.
- (a) Hermaphroditism: True, False
- (b) Transvestism

VI. Miscellaneous.
  (a) Following prostatectomy.
  (b) Albright's syndrome.
  (c) Diabetes mellitus
  (d) Cushing's syndrome

B Diseases of the liver
  I Cirrhosis
  II Hepatitis
  III. Carcinoma
  IV Hæmochromatosis.

C Diseases of the alimentary canal
  Ulcerative colitis

D Malnutrition and renutrition.

E Diseases of the central nervous system.
  I Traumatic paraplegia
  II Friedreich's ataxia.
  III Syringomyelia
  IV Dystrophia myotonica

F Pulmonary disease
  I Bronchogenic carcinoma
  II Tuberculosis
  III Bronchiectasis
  IV Empyema

G Drugs
  Œstrogens
  Androgens
  Chorionic gonadotrophin
  Adrenocortical hormones
  Digitalis
  Radioactive iodine
  Amphetamine

In the pages which follow, an attempt is made to analyse the data of recorded cases of gynæcomastia arising in association with these various diseases In some of the diseases in the above list (e g bronchiectasis) it will be argued that insufficient evidence has so far been presented to establish the association of gynæcomastia and the disease in question as anything more than coincidental Unless the onset and

gynæcomastia are so poorly documented in this respect that the simultaneous occurrence of the two conditions must be regarded, for the present, as fortuitous On the other hand, cases of bronchogenic carcinoma have been described in which the onset was marked by gynæcomastia, and the latter has disappeared within a few days of operative removal of the affected lung

In most of the diseases which cause gynæcomastia, this symptom affects only a small proportion of those who suffer the causative disease For example, a number suffering from traumatic
versal, and no correlation
e, severity or duration of
of cases of bronchogenic

form of stimulation are more likely to show breast development when exposed to a second stimulus of a different nature? Are boys who show gynæcomastia at puberty more likely to develop this symptom if they later suffer traumatic paraplegia or bronchogenic carcinoma? So far the data required to answer such questions are not available.

's symptom disappears when or responds to treatment; breast requires continuous other occasions the cause of yet gynæcomastia persists, xplained by reference to the s of response are encountered. riod of administration of the œstrogens, and the breasts return to normal when treatment stops. When larger doses are used or treatment is continued for longer periods, the gynæcomastia persists in varying degrees for varying periods after the drug is withheld; in some cases a slight degree of breast development persists indefinitely Presumably the response is dependent upon a number of factors, including the nature and intensity of the stimulating agent, the duration of stimulation, the age of the patient when first exposed to stimulation, and the sensitivity of a given breast to a given stimulus

CHAPTER VII

GYNÆCOMASTIA ASSOCIATED WITH PHYSIOLOGICAL STATES

NEONATAL GYNÆCOMASTIA

Microscopic evidence of stimulation is found in the normal neonatal breast and persists for as long as six months Thereafter shrinkage of duct epithelium and desquamation of lining cells occur Neonatal gynæcomastia commonly disappears within two weeks, but in exceptional cases it may persist for six months or even longer A history of neonatal gynæcomastia persisting for several years is sometimes revealed by patients suffering from gynæcomastia during adult life (or by their mothers)

Neonatal gynæcomastia is so common and transient that it has not been studied extensively However, it would be interesting to know whether any correlation exists between neonatal gynæcomastia and the swelling of the breasts commonly seen in males at puberty

Œstrogens have been found in the urine and blood of infants during the first five days of extrauterine life,[4, 5, 6, 7] and it is generally assumed that neonatal gynæcomastia is the result of direct action of mat[illegible] the newborn breast Recent studies have shown [illegible] the urine during the first two or three days after [illegible]

[illegible] neonatal gynæcomastia secretion of colostrum [illegible]ilar experiments have [illegible]wborn male guinea-pigs [illegible]d active secretion from

Prolactin may also play some part in the pathogenesis of neonatal gynæcomastia Lyons[9, 10, 11] developed a method of assay for this hormone which involves a local intradermal crop test in young pigeons, the response being compared with the effect of purified prolactin derived from sheep pituitary glands The urine of newborn infants was subjected to this assay each day for the first seven days of life[10] Of these infants three were male, two of whom showed neonatal gynæcomastia (one with active secretion), the third boy showed neither swelling nor secretion, while the girl showed swelling only In all four infants the urine showed "mammogenic activity", that of the boy with secreting breasts showing greater activity than the others Lyons does not claim that these results are strictly quantitative, but concluded that the newborn baby has in its tissues hormones capable of stimulating the mammary glands, and that secretion may result from the action of prolactin upon [illegible] In addition it has been suggested [illegible]

The activity of mammary tissue in the newborn is part of a general state of

gynæcomastia may presage the occurrence of gynæcomastia later in life. The presence of œstrogens, progesterone and prolactin in the urine of newborn infants provides adequate explanation for the development of alveoli and hence for lactating mammary tissue The elimination of these hormones from the body may account for the appearance of colostrum.

GYNÆCOMASTIA AT PUBERTY

Some degree of breast enlargement is common at puberty and may escape notice unless pain or secretory activity causes the breasts to be examined In most cases this is a transient phenomenon, but sometimes the enlargement is conspicuous and persistent.

Jung and Shafton[12] in 1938 undertook an extensive study of the onset and

areolæ of most normal boys at puberty. The authors referred to this mass as the subareolar node and regarded it as part of normal puberty Jung and Shafton further showed that the subareolar node commonly appears at 13 years of age, reaches its maximal size after about 15 months, maintains this for a further 15 months, and finally disappears, so that by the age of 17 years it is no longer to be found in most normal boys These statements describe the most frequently encountered of many possible variations in onset and duration Jung and Shafton estimated that some enlargement of the breasts can be detected in approximately 77% of normal boys during puberty but in only 15% of men by the age of 20 years In most cases the subareolar node is bilateral

Puberty is sometimes artificially induced by means of chorionic gonadotrophin when this hormone is used to bring about descent of the testis This artificial puberty closely resembles normal puberty except that the sequence of events is sometimes more rapid In about 33% of boys treated with chorionic gonadotrophin between the ages of eight and 12 years,[13] a transitory subareolar node, which closely resembles that described by Jung and Shafton is seen [illegible]

normal puberty

In contrast to the small " button " of breast tissue which appears during puberty in boys, it sometimes happens that a considerable enlargement of one or both breasts occurs, and the organs may reach the size of adolescent female breasts Such

the other is one of degree The subareolar node requires careful examination of the chest before it is detected, while essential gynæcomastia is at least of Grade I severity (see page 15), being obvious on general inspection of the chest Essential gynæcomastia may then be defined as obvious enlargement of the breasts which appears

during an otherwise normal puberty in healthy boys. The subareolar node is excluded from this definition by the words "obvious" and "otherwise normal", because this structure does not produce gross enlargement and because it is seen during normal puberty.

CLINICAL FEATURES

Age of Onset

Essential gynæcomastia makes its appearance between the ages of 12 and 20 years, and it is characteristi
seen, puberty is still incom
at the age of 14 years An
began before the patient's
between 17 and 20 years of age, it was associated with a late and protracted puberty. For example, a patient who first noticed gynæcomastia at 19 years of age had shown some development of pubic and axillary hair at the age of 14 years, but the voice was unbroken and puberty remained incomplete until the age of 19 years, when a

ages are of course unreliable, and most patients find it difficult to recall when they began shaving, etc, but after patient enquiry it became apparent that essential gynæcomastia first appeared *during* puberty

Affected Breast

Essential gynæcomastia more often affects both breasts than either alone Usually both breasts reach the same size, but one may become larger than the other Again the two sides usually enlarge synchronously, but one may precede the other, both eventually reaching the same size (Table I) Among unilateral cases the left and right breasts are affected with equal frequency Some authors describe a high percentage of unilateral cases of gynæcomastia, but this is not found among patients in whom gynæcomastia appears during puberty[14, 15]

TABLE I
Breast Development in Gynæcomastia

Bilateral and Symmetrical Cases (23)		Asymmetrical Cases (9)	
Grade	Number of Cases	Grade	Number of Cases
I	6	III and o	3
II	9	III and II	2
III	8	II and o	4

Severity

Table I shows the severity of gynæcomastia among the Guy's Hospital patients These observations indicate that essential gynæcomastia most commonly brings about the appearance of two well-developed breasts, which, however, fall short in size of the normal breasts of nulliparous young women Asymmetrical cases may result from the presence of one normal breast, less often from the unequal development of two affected breasts Three patients complained of secretion from the breasts

Pain

The breasts were painful in the early stages of essential gynæcomastia in 12 of 32 patients. In five the pain was intermittent, but persisted as long as the breasts remained enlarged Intermittent pain was often associated with irritation from clothing (e g , braces) or changes in body temperature, but in some cases it was spontaneous Four patients stated that the breasts became acutely tender when they became overheated during exertion, in a hot bath, or in an overheated room. The incidence of pain was not related to the age at onset of gynæcomastia.

These findings recall the work of Jung and Shafton,[12] who found that the subareolar node appeared for the first time most frequently at the age of 13 years and that it reached its maximal development after a further 15 months. The authors stated that the subareolar node was detected at the age of 13 years by careful

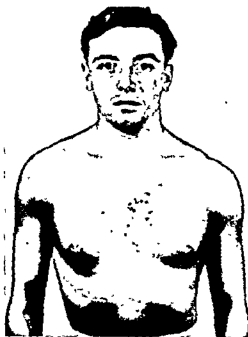


FIGURE 4
Essential gynæcomastia associated with acne

examination The Guy's Hospital patients most frequently noticed essential gynæcomastia at the age of 14 years, but perhaps this would have been detected earlier by c…
of normal l…
age and ur…
normal puberty

Acne

less muscular build, showed considerably less body hair, and were less interested in

such manly activities as sport, preferring more artistic recreations. These observations merely represent a general impression and cannot readily be subjected to measurement, but certainly about half of those a
also showed severe acne It is worth mentioning
severe acne may occasionally be due to the use
intractable acne, this is a point of some diagnostic importance

Natural History

At present the ætiology of essential gynæcomastia remains in doubt, and no rational endocrine treatment has been discovered It is, however, common practice

treatment, whether surgical or conservative The value of surgery is therefore closely related to the natural history of the condition If it can be shown that this benign condition undergoes remission shortly after it appears in a high proportion of cases, surgery is unnecessary On the other hand, if essential gynæcomastia, once it has developed, tends to persist indefinitely, then surgery is to be advised

TABLE II *
The Natural History of Essential Gynæcomastia

Duration of Follow-up (Years)	Number of Patients	
	Untreated (16)	Submitted to Operation (18)
1	4	4
2	2	3
4	1	—
6	—	6
8	4	2
>8	5	3

Among 34 patients suffering from essential gynæcomastia at Guy's Hospital only two showed spontaneous remission In the remaining 32 cases the swelling reached its maximal development during a period of between six and 24 months, and thereafter remained constant in size

Table II shows the result of follow-up studies in these 34 patients The size of the breasts was compared by means of photographs taken at first attendance and at follow-up Cases in which follow-up was artificially terminated by operation are treated separately These studies therefore indicate the minimal duration of gynæcomastia In no case was partial, unilateral or temporary regression noticed

These studies indicate that essential gynæcomastia is a condition in which spontaneous remission cannot be anticipated, at least during the first eight years after its appearance, and such a finding will influence the treatment of the condition (Chapter XVI)

Past Health

No finding of ætiological importance was made in the previous health of patients affected by essential gynæcomastia Mumps had affected nine out of 34 of the patients in the Guy's Hospital series, but none suffered from orchitis Traumatic lesions of the testis, prolonged fevers and the use of drugs known to cause gynæcomastia were not discovered

Three patients had suffered from protracted neonatal gynæcomastia The first showed this condition for two years with profuse secretory activity At the age of 14 years the patient developed marked (Grade III) painless gynæcomastia,

* The two patients showing spontaneous remission are not included in this table (see page 37)

atient's brother* was similarly affected, astia, with Grade III gynæcomastia at the age of 17 years The second omastia and painless gynæcomastia (Grade I) at sixteen years of age, showing spontaneous remission at the age of 18 years.



FIGURE 5
An example of spontaneous remission of essential gynæcomastia of Grade I severity
(A) Aged 14 years (B) Aged 20 years

The thirc two years, and then painless the age of 12 years, and was tient stated that his only bro that his cousin also suffered from gynæcomastia (Table III)

TABLE III
The Relationship between Neonatal, Essential and Involutional Gynæcomastia

Case	Neonatal Gynæcomastia	Essential Gynæcomastia		Family History		
		Between the Years of	Outcome of Gynæcomastia	Relation	Nature of Gynæcomastia	Outcome of Gynæcomastia
VII	Severe and protracted	14 and 16	Disappeared spontaneously	Only brother	Neonatal and essential	Disappeared spontaneously
XVIII	—	14 and 22	Operation	Father	Essential and involutional	Disappeared spontaneously
XIX	—	15 and 17	Persisted	Only brother	Essential	Persistent (>8 years)
XXIII	Severe and protracted	16 and 18	Disappeared spontaneously	Only brother	Neonatal and essential	Disappeared spontaneously
XX	Severe and protracted	12 and 18	Operation	First cousin	Neonatal and involutional	Disappeared spontaneously

Whether these findings indicate a special type of gynæcomastia occurring in certain families cannot at present be stated

* The relatives of these three patients are not included in the present series

Urinary Œstrogens

Table IV shows the results of assays performed upon seven patients suffering from essential gynæcomastia. Unfortunately, present methods of œstrogen assay leave much to be desired, especially when the levels to be measured are low. Moreover, the range of normal during puberty has not been established with great accuracy. However, six normal boys between the ages of 14 and 16 years, each of whom showed some signs of puberty, but in whom puberty was not complete, showed the following range of urinary œstrogens, measured by the same method (see page 17): œstrone, <0·5 µg. per 24 hours; œstradiol, <2·0 µg per 24 hours; œstriol, 2–11 µg. per 24 hours.



FIGURE 6

(A) The appearance of the germinal epithelium in the testis of a normal boy, aged 16 years (B) The testis of a boy, aged 16 years, suffering from essential gynæcomastia This testis is normal, but the tubules are highly cellular

In adult males urinary œstrone may reach 1·0 µg per 24 hours It is unwise to be dogmatic about the range of normal at such low levels as these However, in Cases I and XIX the level of œstrone recorded in Table IV exceeds that found among

of the onset of gynæcomastia

Testicular Biopsy

In general, testicular biopsy is normal in essential gynæcomastia Frequently the tubules appear to be crowded with germinal cells in the manner described by

Semen

The results of sperm counts and of motility tests and the appearance of the spermatozoa themselves are all normal in essential gynæcomastia

Histology of the Breast

The microscopic appearance of the breast in essential gynæcomastia does not differ from that seen in other forms of gynæcomastia (page 22) and consists essentially of duct hyperplasia and increase in the cellularity of the stroma without alveolar development. These findings are based upon 18 patients submitted to operation at Guy's Hospital

OTHER INVESTIGATIONS

The results of other investigations, including liver function tests, estimation of basal metabolic rate, full blood count and X-ray examination of epiphyses, are also within normal limits.

ÆTIOLOGY

Essential gynæcomastia occurs at the same age as and under similar circumstances to the subareolar node and the enlargement of the female breast The development of the breasts in girls at puberty appears to result from the direct action of hormones upon the mammary tissue These statements raise three questions: Is the subareolar node strictly analogous to enlargement of the female breast, that is, does it result from the same cause? If so, why is the development of the male breast cut short while that of the female continues until the dimensions of the adult female breast are attained? Is essential gynæcomastia to be regarded as an exaggeration of the normal development of a subareolar node?

The first changes in the female breast at puberty involve duct hypertrophy and increase in the cellularity of the breast stroma, but without alveolar development These changes are thought to result from the direct action of œstrogens upon the breast in the presence of a normal anterior pituitary gland (page 24) Progesterone probably does not play an important part at this stage, since the first menstrual cycles are anovulatory, but it is likely that progesterone subsequently produces alveolar development[19] These observations may be regarded as circumstantial evidence in favour of the view that the subareolar node is due to the direct action of œstrogens upon the male breast at puberty The quantitative difference between the response of the mammary tissue of the two sexes is presumably due to greater concentration of œstrogens in the female, or to some inherent difference in the end-organs which makes the response greater in the case of the female or to both factors

The other hormones which could be considered as possible causes of the subareolar node and of essential gynæcomastia are androgens Although cases are known in which treatment with androgens leads to gynæcomastia (page 125), this is not a common sequel of androgen therapy On the other hand, gynæcomastia regularly follows the administration of œstrogens in boys and men

Evidence in favour of the view that essential gynæcomastia is an exaggeration of the normal breast development of boys is entirely circumstantial The two phenomena occur at the same age and under the same circumstances—that is, during puberty In spite of the lack of more positive evidence, it is difficult to escape the conclusion that essential gynæcomastia results from the direct action of hormones on the breast If this is the case, two possibilities must be considered—namely, a hypersensitivity of mammary tissue to normal concentrations of some hormone or hormones on the one hand, or the presence of excessive concentrations of one or more hormones on the other hand A third possibility exists—namely, that breast stimulation results from the action of an abnormal hormone, i e one which is not present in normal individuals For the third possibility there is no clinical or

laboratory evidence, such a hormone could produce only one demonstrable effect—namely, breast stimulation; and until some positive evidence for its existence is forthcoming, this possibility will be rejected

The next problem is the nature of the hormone concerned Œstrogens and

serious objection to the case for androgens as the important cause of essential

These two patients were seen nearer
upon whom this assay was performed
of the limitations of the methods u

mastia This could suggest that such individuals are subjected to greater concentrations of maternal or placental œstrogens, which produce greater development of

c
f

ls to
case
the
the
concentration of these hormones declines This is further suggested by the observation that the only two patients with raised urinary œstrogens were those examined soon after the onset of gynæcomastia.

By contrast, the majority
gynæcomastia, or a history o
spontaneous remission. The
a special type of essential gynæcomastia, and these points may be of some prognostic and ætiological significance

The presence of severe acne in about half the patients affected by essential gynæcomastia, and the observation that these patients are conspicuously muscular and virile individuals, might be taken as indirect evidence in favour of excessive androgen secretion However, such evidence is not supported by consistently high levels of 17-ketosteroid excretion, and since the Leydig cells appear to represent the source of both œstrogens and androgens (page 25),[18] stimulation of these cells would produce androgenic effects, and gynæcomastia may represent the only effect of the œstrogens concurrently produced which can be detected clinically

A number of workers have endeavoured to show that
is associated with a disturbance in
Nathanson,[21] for example, has expl
in œstrogen assays make conclusior
they are converted into ratios
, when in reality in the case of

In short, it is *tentatively* concluded that the subareolar node is due to the action of testicular œstrogens upon the breast and is a normal phenomenon. In a small number of boys this response is exaggerated as the result of higher œstrogen levels or of greater sensitivity of the breast (or both). This abnormal response produces *essential gynæcomastia*.

The management of essential gynæcomastia is discussed in Chapter XVI, where a strong case will be made for early surgical treatment

INVOLUTIONAL GYNÆCOMASTIA

When gynæcomastia first appears after middle age, it usually points to some serious under[illegible] this time of life is not always so sinister, [illegible] in libido and sexual potency (*Figure 7*) [illegible] be overlooked because of the great variatio[illegible]l period of their lives Some are affected by a male climacteric, while in others the approach of old age is so stealthy as to defy exact localization. Gynæcomastia which first appears at or shortly after



FIGURE 7

An example of involutional gynæcomastia (*a*) Shows gynæcomastia of grade III severity in a man of 56 years (*b*) Shows testicular biopsy taken from the same patient, basement membrane, spermatogenesis and Leydig cells are normal (*c*) Shows high power field of the same specimen

the period of sexual decline in men who are otherwise healthy can be referred to as involutional gynæcomastia The condition is not common, and the diagnosis is justified only after careful examination and investigation have eliminated any underlying disease The diseases to be eliminated in this way are those mentioned as *causes of gynæcomastia in the succeeding chapters of this* book *Involutional* gynæcomastia is illustrated by the following case history

[illegible] from about the age of 52 years [illegible] At about the same age he [illegible]ood health in the past and, [illegible] abnormal *The results of* chest X-ray examination, blood count, liver function tests, estimation of basic metabolic rate, [illegible] The patient was seen [illegible] this time The investi[illegible]ears of observation and [illegible]

The difficulty in diagnosing involutional gynæcomastia lies in establishing the fact that the patient is free of any serious underlying disease By contrast, it is relatively easy to eliminate serious underlying disease at puberty in the case of essential gynæcomastia The diagnosis of involutional gynæcomastia is therefore reached by exclusion and should be supported by a period of observation

CLINICAL FEATURES

In a series of 10 patients the age of onset of the gynæcomastia was between 52 and 66 years It was associated with loss of libido and potency in every patient, but only half of those affected complained of other symptoms such as hot flushes, lethargy and irritability. The condition is usually bilateral and symmetrical, and may undergo remission (complete or partial) The previous history of libido, potency and fertility are not remarkable, and past health has usually been good.

SPECIAL INVESTIGATIONS

gonadotrophic hormones is extremely variable in normal men Examination of semen has not revealed any consistent abnormality, and the results of testicular biopsy are normal for the patient's age (Figure 7).

ÆTIOLOGY

It is at present not possible to discuss the ætiology of involutional gynæcomastia Little is known about the quantitative and qualitative changes in endocrine activity during the time of sexual involution in men.

six years of complete sexual inactivity. The sudden return of sexual activity was associated with painful gynæcomastia, interval of between one and two years associated with loss of libido and a ret provide an example of a phenomenon to be encountered in later chapters of this book—namely, the appearance of gynæcomastia at a time when sexual activity reappears after a period of loss of erections and libido (page 113). This sequence of events has something in common with gynæcomastia at puberty, except that puberty represents the first episode of gonadal stimulation rather than a *reawakening* of sexual activity In one patient studied soon after the onset of this form of involutional gynæcomastia, urinary œstrogens were found to be too low to measure by the method described on page 17

MANAGEMENT

The management of involutional gynæcomastia is discussed in Chapter XVI, where a conservative policy is advocated

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[8] ABRAHAM, G (1930), "*Hormone und Brustdrüse*", *Med Klin*, 28 164

In short, it is tentatively concluded that the subareolar node is due to the action of testicular œstrogens upon the breast and is a normal phenomenon. In a small number of boys this response is exaggerated as the result of higher œstrogen levels or of greater sensitivity of the breast (or both). This abnormal response produces essential gynæcomastia.

The management of essential gynæcomastia is discussed in Chapter XVI, where a strong case will be made for early surgical treatment

INVOLUTIONAL GYNÆCOMASTIA

When gynæcomastia first appears after middle age, it usually points to some serious underlying cause However, gynæcomastia at this time of life is not always so sinister ; it may appear together with a decline in libido and sexual potency (Figure 7) The significance of this association may be overlooked because of the great variation with which men enter the involutional period of their lives. Some are affected by a male climacteric, while in others the approach of old age is so stealthy as to defy exact localization Gynæcomastia which first appears at or shortly after



FIGURE 7

An example of involutional gynæcomastia (*a*) Shows gynæcomastia of grade III severity in a man of 56 years (*b*) Shows testicular biopsy taken from the same patient, basement membrane, spermatogenesis and Leydig cells are normal (*c*) Shows high power field of the same specimen

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causes of gynæcomastia in the succeeding chapters of this book Involutional gynæcomastia is illustrated by the following case history

The patient noticed a gradual decline in libido and potency from about the age of 52 years This was associated with hot flushes, irritability and loss of energy At about the same age he noticed painful bilateral gynæcomastia The patient had enjoyed good health in the past and, apart from gynæcomastia, physical examination revealed nothing abnormal The results of ... function tests, estimation of basic metabolic rate,
mal limits The patient was seen
od during this time The investi-
the five years of observation and

The difficulty in diagnosing involutional gynæcomastia lies in establishing the fact that the patient is free of any serious underlying disease *By contrast, it is* relatively easy to eliminate serious underlying disease at puberty in the case of essential gynæcomastia The diagnosis of involutional gynæcomastia is therefore reached by exclusion and should be supported by a period of observation

CHAPTER VIII

GYNÆCOMASTIA ASSOCIATED WITH DISEASES OF THE TESTIS

In 1894 Williams[1] suggested that diseases of the testis which cause destruction of testicular tissue could produce gynæcomastia This led to the idea that the testis protects the male body from a tendency to develop certain female characteristics Since that time many workers have concluded that the testis plays an important part in the ætiology of gynæcomastia

The following diseases of the testis may be associated with gynæcomastia ·

(1) Certain forms of hypogonadism
(2) Tumours of the testis
(3) Leprous orchitis
(4) Mumps orchitis
(5) Bilateral orchitis
(6) Radiation of the testis
(7) Undescended testes
(8) Castration
(9) Traumatic lesions of the testis
(10) Certain unilateral testicular lesions

HYPOGONADISM

Certain forms of male hypogonadism are commonly associated with gynæcomastia, and since a number of rather confusing systems for the classification of these conditions are at present in use, it is necessary to begin with a brief account of the nomenclature to be used

Hypogonadism may result from lesions of the adenohypophysis or from diseases of the testis In rare instances, the possibility of an inherent resistance of the tissues or end-organs to the action of normal quantities of hormone may be responsible for the appearance of signs and symptoms which resemble those encountered in hypogonadism this possibility is not relevant to the problem of gynæcomastia The signs and symptoms of hypogonadism vary not only according to the site of the lesion, but also with the age of the patient at the onset of the condition For example, failure of Leydig cell function before puberty leads to the gross abnormalities of eunuchoidism and failure of the development of secondary sexual characteristics On the other hand, when failure of Leydig cell function first occurs during adult life, the regression of established secondary sexual characteristics is remarkably slow

When hypogonadism is the result of failure of the adenohypophysis to secrete sufficient gonadotrophic hormones, the urinary output of gonadotrophins is low, and the capacity of the testis to respond to pituitary stimulation is indicated by the response to injections of chorionic gonadotrophin, which brings about the appearance of secondary sexual characteristics or maintains sexual activity in the case of adults When hypogonadism is due to testicular failure, urinary gonadotrophin levels are higher than normal, and the testis is incapable of responding to chorionic gonadotrophin

Classification of hypogonadism is based upon these observations, and Heller, Nelson and Roth[2] proposed a useful system of classification in 1948 This system, which is illustrated in Table V, has been criticized on the grounds of over-simplification, but until ætiological factors are better understood it provides a useful skeleton for descriptive purposes

[9] LYONS, W. R (1937), "Preparation and Assay of Mammotrophic Hormone", *Proc Soc. exper Biol & Med*, 35 · 645
[10] LYONS, W R (1937), "Hormonal Basis for 'Witches' Milk", *Proc Soc exper Biol & Med*, 37 · 207
[11] LYONS, W. R, and PAGE, E (1935), "Detection of Mammotropin in Urine of Lactating Women", *Proc Soc exper Biol & Med*, 32 . 1049
[12] JUNG, F T, and SHAFTON, A L. (1938), "Mastitis, Mazoplasia, Mastalgia and Gynecomastia in Normal Adolescent Males", *Illinois M J*, 73 . 115
[13] DE MOWBRAY, R (1953), "The Treatment of Infantilism", D M thesis, Oxford
[14] MENVILLE, J G (1933), "Gynecomastia", *Arch Surg*, 26 1054
[15] KARSNER, H T (1946), "Gynecomastia", *Am J Path*, 22 235
[16] BISH
[17] DAV ... *nt M J*, 2 . 676
[18] HEL ... C, and NELSON, W O (1952), ... d Classification of Testicular ... ", *Ann New York Acad Sc*, 55 ...
[19] ... don, 2 . 525
[20] ... on Mammary Gland of
[21] ... ase Urinary Excretion ... in Adolescent Mastitis
[22] ... d CANLORBE, P (1956), ... *e hôp*, *Paris*, 32 1763

It will be seen that gynæcomastia occurs in cases of testicular failure supervening before or during puberty but not in other forms of testicular failure. Testicular failure before or during puberty is of two types—namely, prepubertal testicular failure and Klinefelter's syndrome Prepubertal testicular failure is a condition in which no functioning testicular tissue can be found in the scrotum, while Klinefelter's

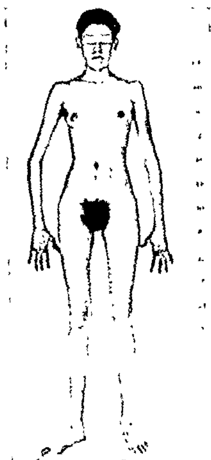


FIGURE 8
Prepubertal testicular failure in a patient aged 18 years The characteristic eunuchoid proportions and gynæcomastia (grade II) are well shown The development of pubic hair increased after treatment with testosterone before this photograph was taken

syndrome is associated with characteristic histological changes in the testis. Prepubertal testicular failure is also called prepubertal non-castrate eunuchoidism, and the word *prepubertal* is spelled *prepuberal* by most American authors Throughout this book the English spelling is used, and the name *prepubertal testicular failure* is preferred

This classification does not include testicular failure due to specific ætiological agents, such as mumps orchitis, traumatic lesions, leprosy, castration, etc Many

TABLE V

A Classification of Male Hypogonadism

Time of Onset	Urinary Gonadotrophins	Response to Chorionic Gonadotrophin	Failure of Other Pituitary Functions	Skeletal Development	Gynæcomastia	Size of Testes	Testicular Biopsy	Potency	Diagnosis
Before or During Puberty	Low	Positive	Yes	Dwarfism	Absent	Half adult size	Tubules infantile Leydig cells infantile	Poor	Panhypopituitarism
	Low	Positive	No	Eunuchoidism	Absent	Half adult size	Tubules infantile Leydig cells infantile	Poor	Hypogonadotrophic hypogonadism
	High	Nil	No	Eunuchoidism	Present or absent	Absent	Absent (Wolffian *remnants*)	Poor	Prepubertal testicular failure
	High	Nil	No	Normal	Present	One-quarter adult size	Hyalinization of *tubules* Clumping of Leydig cells	Poor	Klinefelter's syndrome
After Sexual Maturity	Low	Positive	Yes	Normal	Absent	Three-quarters adult size	Tubules and Leydig cells return to an infantile state	Poor	Adult panhypopituitarism
	Low	Positive	No	Normal	Absent	Three-quarters adult size	Tubules and Leydig cells return to an *infantile state*	Poor	Adult hypogonadotrophic hypogonadism
	High	Nil	No	Normal	Absent	Normal	Atrophy absence or disorganization *of* tubules or Leydig cells	Poor	Adult hypergonadotrophic hypogonadism
	High	Nil	No	Normal	Absent	Normal to three-quarters adult size	Tubules are small or hyalinized, sloughing of germinal epithelium	Normal	Adult seminiferous tubular failure

distinctions are academic, and a patient may be regarded as suffering from functional prepubertal testicular failure when a biopsy taken during adult life reveals either Wolffian duct derivatives or rudimentary testes, provided that the scrotal contents are less than 1·0 cm. in diameter and that the other features of the syndrome are present Until more is known of the ætiological factors which cause failure of the



FIGURE 9

The scrotal contents in prepubertal testicular failure (A) Vasa efferentia are seen, but seminiferous tubules are absent (B) *High power view of* vas efferens lined by columnar epithelium whic
(C) Poorly devel
Leydig cells can
tubules lined by
membrane show

other classifications of hypogonadism have been devised, but as these are usually complicated by the inclusion of lesions which do not cause gynæcomastia, the system of Heller, Nelson and Roth is considered adequate for present purposes

Prepubertal Testicular Failure

In 1943 Heller and Nelson described a syndrome which they called functional prepubertal castration in males This is characterized by (*a*) the presence of Wolffian duct derivatives in the scrotum but absence of functional testes, (*b*) sexual infantilism, (*c*) some delay in osseous development, (*d*) high urinary gonadotrophin excretion, and (*e*) response to treatment with testosterone but not with chorionic gonadotrophin

This syndrome may result from a variety of causes, but the essential feature is that total failure of the testis (germinal and endocrine) appears before puberty [illegible] o treatment with [illegible] pituitary failure, [illegible] that the tissues themselves are not inherently resistant to the action of androgens That the ætiological factors concerned operate before puberty is indicated by the presence of eunuchoidism The condition closely resembles surgical castration before puberty and is so named as to exclude this possibility.

The ætiological factors responsible for this syndrome are varied Some cases appear to have followed operations for inguinal hernia before puberty, and it has been suggested that during operation the blood supply to the testis has suffered In other cases a sclerosis of unknown ætiology affects the walls of the tubules, which as a result fail to develop fully In yet another group failure of union between the Wolffian duct and the testis may occur, so that derivatives of the former structure may appear in the scrotum unaccompanied by the testes, which remain in the abdomen. Sometimes failure of union between the Wolffian duct and the testis results in the appearance of the epididymis alone in the scrotum [9, 10, 11, 12, 13] Finally, some cases may be due to congenital failure of the testes to develop (anorchia)

Before the diagnosis of this syndrome can be established, testicular biopsy is necessary in order to demonstrate the absence of functional testicular tissue Consideration of the ætiological factors involved will show that the results of biopsy are varied In cases following surgical operations upon the inguinal canal and in those associated with sclerosis of the tubules, some testicular tissue will be found That this tissue is not functional will be indicated by the rudimentary appearance of the tubules and by the absence of normal Leydig cells These findings will be reflected by the presence of eunuchoidism and sexual infantilism These clinical signs will, moreover, prove that the causal factors operated before puberty, thereby establishing the diagnosis of prepubertal testicular failure In cases resulting from failure of union between the Wolffian ducts and the testis, biopsy will reveal no testicular elements but [illegible]

germinal epithelium or Sertoli cells (Figure 9) Again, immature epididymal tissue or ductus deferens may be found [8] When testicular biopsy reveals epididymal tissue, it may be argued that biopsy has been unsatisfactory and that testicular tissue, although present in the scrotum, has not been located by the operator, who has simply cut into the epididymis That this argument is realistic is shown by the appearance of epididymal tissue without testis in the biopsy of normal gonads However, if the scrotal contents are less than 1·0 cm in diameter, and if bilateral testicular biopsy reveals some form of Wolffian duct derivatives but no testis, it is highly probable that functional testicular tissue is absent from the scrotum Similarly, the diagnosis of anorchia during life can be substantiated only by a major surgical exploration of the scrotum, inguinal canals and abdomen For the most part these

present Until more is known of the ætiological factors which cause failure of the



FIGURE 9

TABLE VI

Clinical Features of Patients with Prepubertal Testicular Failure

Case Number	Height (Inches)	Weight (Pounds)	Span (Inches)	U S	L S	Erections	Emissions	Pubic Hair: Distribution	Pubic Hair: Amount	Axillary Hair	Beard	Temporal Hair-line	Voice	Age (when first seen)
XLVII	66½	123	70	30½	36	Absent	Absent	Female	Scanty	Scanty	Poor	No recession	High	25
XLVIII	73	238	74¾	35¼	37¾	Some	Absent	Female	Scanty	Scanty	Poor	No recession	High	18
L	73	176	74½	35¼	37¾	Some	Few	Female	Scanty	Scanty	Poor	No recession	Low	19
LI	71¾	173	75½	33½	38¼	Some	Absent	Female	Scanty	Normal	Poor	No recession	Low	21
LII	74	134	76¾	33¾	40¼	Some	Few	Female	Scanty	Normal	Poor	No recession	Low	18
LIII	69	143	71	33½	35½	Some	Few	Female	Scanty	Scanty	Poor	No recession	High	19
LIV	71	211	72½	34	37	Some	Absent	Female	Scanty	Scanty	Normal	No recession	Low	53
LVI	67½	152	69¼	32½	35	Some	Absent	Female	Normal	Scanty	Poor	No recession	High	25
LVII	74	140	75¾	35¼	38¾	Some	Few	Female	Scanty	Normal	Poor	No recession	High	20
LVIII	72½	158	74	34	38½	Few	Absent	Female	Scanty	Scanty	Normal	No recession	High	22
LV	63	143	65	30½	32½	Few	Absent	Female	Normal	Scanty	Poor	No recession	Low	22

TABLE VII
Gynæcomastia in Prepubertal Testicular Failure

Case Number	Age at Onset (Years)	Severity (Grade)	Duration at Follow Up (Years)	Severity at Follow Up (Grade)	Duration at Operation (Years)
XLVII	14	I	22	I	—
XLVIII ..	18	III	—	—	12
L	19	I	4	I	—
LI .	20	I	5	I	—
LII	15	I	6	I	—
LIII	19	I	—	—	1
LIV	14	III	39	III	—
LVI	16	I	—	—	7
LVII	20	I	6	I	—
LVIII	14	I	16	I	—
LV	21	I	—	—	2

testis before puberty, the name prepubertal testicular failure is a convenient way of referring to this heterogenous group of conditions The disease which is most likely to cause difficulty in diagnosis is hypogonadism as an isolated manifestation of pituitary failure. In this condition urinary gonadotrophins are low, the testis shows arrest of spermatogenesis in the presence of well-formed tubules, and the condition responds to treatment with chorionic gonadotrophin

TABLE VIII
Duration of Gynæcomastia in Prepubertal Testicular Failure

Duration of Gynæcomastia (Years)	Patients Submitted to Operation (4)	Patients Not Submitted to Operation (7)
1–5	2	2
6–11	1	2
12–20	1	1
>20	—	2

The clinical and laboratory data of 11 patients who fulfilled the requirements of prepubertal testicular failure are shown in Tables VI, VII, VIII and IX It will be seen that in this syndrome gynæcomastia is usually mild (Grade I) and first appears between the ages of 14 and 21 years (Table VII), once it is established, gynæcomastia in prepubertal testicular failure shows no tendency to spontaneous remission (Table VIII) The principal symptoms of which these patients complain are connected with failure of development of the secondary sexual characteristics, which proves such a source of embarrassment that the gynæcomastia, which is mild, is not regarded so

TABLE IX
Laboratory Investigation in Prepubertal Testicular Failure

Case Number	17-Ketosteroids (Mg per 24 Hours)	Urinary Gonadotrophins (Mouse Units per 24 Hours)	Semen (Number of Tests)	Testicular Biopsy	Epiphyses		Urinary Œstrogens (µg per 24 Hours)		
					Bone Age*	Chronological Age	Œstrone	Œstradiol	Œstriol
XLVII	12·3 21·0	>48<64 >96	Azoospermia (3)	Vas deferens	Adult	25	—	—	—
XLVIII	6·9 7·0	>96 >96	Azoospermia (2)	Vas deferens	Adult	21	—	—	—
L	13·0 11·0 15·0 12·4	>96 >96 >96	Azoospermia (2)	Poorly developed tubules	Adult	21	1·7	0·3	9·0
LI	16·0 15·0 9·0 20·0	>24<32 >64<96 >96	Azoöspermia (3)	Vas deferens	Adult	22	1·1	0·2	12·0
LII	6·0	>96	Azoospermia (2)	Immature epididymis	17	20	0·5	4·1	2·0
LIII	11·7 12·8	>128 >96	Azoospermia (2)	Vas deferens	17–19	22	—	—	—
LIV	3·7 13·0	>96 >68<96	No ejaculate	Vas deferens	Adult	53	—	—	—
LVI	15·4 8·8 9·0	>96 >96 >96	No ejaculate	Epididymis	Adult	25	—	—	—
LVII	10·2 12·0	>16<32 >96	Azoöspermia (3)	Poorly developed tubules	17	26	—	—	—
LVIII	10·2 9·4	>16<32 >96	No ejaculate	Epididymis	Adult	22	—	—	—
LV	10·0 12·0	>64<96 >96	Azoöspermia (3)	Vas deferens	20	25	—	—	—

* It is probable that some of these patients had been given hormones before they were seen at Guy's Hospital. This would no doubt have advanced their epiphysial maturation.

seriously As a result the age of onset and other features of the breast development are not clearly remembered. However, it can be stated that the gynæcomastia is painless and not associated with secretion from the nipples. These patients all showed smooth clear skins and maintained that they had never suffered from acne

It is inevitable that some patients who turn out to be examples of prepubertal testicular failure are regarded as suffering from undescended testes before puberty. Unless small nodules are felt in the scrotum, it is scarcely possible to distinguish the two conditions (before puberty), and it is not surprising that two of the present series of patients received hormone treatment in the hope of causing descent of the testes. This treatment did not cause the associated gynæcomastia, since breast development preceded hormone therapy by more than two years When chorionic gonadotrophin is the hormone used, one would not expect gynæcomastia to occur in cases of prepubertal testicular failure, because this hormone is thought to cause breast development by stimulating the activity of the Leydig cells (page 25)

Prepubertal testicular failure is not familial, and except in the case of patients submitted to herniorrhaphy, the past health reveals nothing of interest. The 17-ketosteroid excretion was normal and the level of urinary gonadotrophins high in every patient The three patients in whom urinary œstrogens were estimated (Table IX) showed levels within or just beyond the normal range Histological changes seen in the breast are those found in other forms of gynæcomastia (see page 22)

Pathogenesis

Boys subjected to surgical castration before puberty do not develop gynæcomastia On the other hand, about one-half of those who suffer prepubertal testicular failure show a mild degree of breast stimulation[2] In those cases of prepubertal testicular failure due to anorchia or to failure of union between testis and Wolffian duct, it may be assumed that the patient lacks any functional testicular tissue In the absence of any evidence to show that the adrenal cortex in this condition is responsible for the secretion of excessive quantities of œstrogens or androgens, it is difficult to see how breast stimulation in cases of this syndrome could result from excessive quantities of either of these groups of hormones It seems logical to conclude that the difference (from a functional point of view) between prepubertal testicular failure and surgical castration before puberty must lie in the activity of testicular tissue before the time of surgical castration There is good reason to believe that the testis is active before birth,[3] and while still situated within the abdomen, this structure directs the development of the Wolffian ducts at the expense of the Mullerian ducts and influences the differentiation of the external genitalia[4] In this way it is possible to account for the ætiology of Turner's syndrome, which is associated with female phenotypic or functional sex in individuals with male chromosomal sex[4, 5, 6, 7]

It is not at present possible to do more than guess at the pathogenesis of prepubertal testicular failure If the testes were absent or functionless during intrauterine life, one would expect such individuals to develop female phenotypic sex We can only suppose that the gonads are present in the abdomen until after the time of differentiation of the genital ducts and external genitalia is accomplished, and that they subsequently undergo some destructive process Perhaps the destruction of the testes exposes the breasts to some feminizing influence during the last stages of intrauterine life, which renders the mammary tissue unduly susceptible to the influence of the small quantities of œstrogens or to the androgens secreted at puberty by the adrenal cortex Most patients with Turner's syndrome do not show breast development at puberty, but the mammary gland responds to the administration of œstrogenic hormones However, in some patients affected by Turner's syndrome slight breast development with rudimentary nipples is seen at puberty, and this would no doubt pass for a mild degree of gynæcomastia in the case of male patients[8] Prepubertal testicular failure is a heterogeneous condition, and until

luce this syndrome the patho-
No doubt future studies of
e, although 11 cases reported
by Nelson[103] all showed male nuclear sex.

The patients with prepubertal testicular failure reported by Heller and Nelson[2] were not excessively tall, unlike those affected by other forms of eunuchoidism. The heights of their patients were between 58¾ in. and 70¾ in. In the present series the range was 63 in to 74 in. (five of 11 patients being taller than 72 in). At present it is not possible to account for this difference

Certain features of prepubertal testicular failure remain puzzling In the absence of testicular tissue it might be expected that pubic and axillary hair would be absent and 17-ketosteroid excretion low, as in prepubertal pituitary failure. However, there is good evidence in animals to show that castration soon after birth produces adrenocortical hyperfunction with increased production of androgens[104, 106] There is further evidence of a sort of reciprocity between testicular and adrenal androgens, as for example the fall in urinary excretion of the metabolites of adrenal androgens which follows the administration of 17-methyl testosterone[105]; this substance is not metabolized to 17-ketosteroids. Presumably, therefore, some compensatory increase in adrenal androgen output accounts for the ultimate (but delayed) fusion of epiphyses (the delay permitting growth hormone to produce eunuchoidal changes in the skeleton), for the development of sex hair and for the normal 17-ketosteroid excretion in patients suffering from prepubertal testicular failure

KLINEFELTER'S SYNDROME

In 1942 Klinefelter, Reifenstein and Albright[14] described the condition which is generally referred to as Klinefelter's syndrome This syndrome was said to consist of gynæcomastia, small testes, azoöspermia, evidence of normal to moderately reduced Leydig cell function, increased excretion of pituitary gonadotrophins and (usually) a reduced excretion of 17-ketosteroids This description was based upon a series of nine patients, each of whom had been quite normal until puberty, which began between the ages of 12 and 14 years Gynæcomastia was present in every case and first appe
was of Gr
paper and
in two

The testes were uniformly small and symmetrical throughout the group, the average size being 1·5 x 1·0 x 0·5 cm , and the patients stated that their testes had always been small Three patients had never ejaculated, and of the remaining six four are known to have shown azoospermia In eight of the patients Leydig cell
f the voice, the distribution
adotrophins were uniformly
subnormal " Testicular
biopsies were always abnormal The tubules ... between two extremes in different patients Some cases showed partial hyalinization and defective spermatogenesis in certain tubules, while other cases showed extensive hyalinization of all the tubules and no cells within the tubular remnants Between the two extremes intermediate states occurred, in which hyalinization was moderate and only Sertoli cells remained inside the tubules This hyaline tissue stained pink with eosin and like collagen with aniline blue In no instance was normal spermatogenesis present
The authors state that,
ss than normal, owing
ct the interstitial cells
to be 40 times as numerous as in the normal testis

Albright and his colleagues believed that the occurrence of normal Leydig cells in the presence of defective spermatogenesis and raised urinary gonadotrophins was best explained by the existence of a second testicular hormone secreted by the germinal epithelium—the so-called "X" hormone. By analogy with the female, follicle-stimulating hormone (FSH) promotes spermatogenesis and at the same time stimulates the secretion of "X" hormone, instead of stimulating the maturation of the Graafian follicle and indirectly leading to the production of œstrogens "X" hormone controls the pituitary secretion and/or release of follicle-stimulating hormone, and lack of this "X" hormone, resulting from tubular damage, would lead to raised urinary gonadotrophins

The histology of the breast in one of these cases of Klinefelter's syndrome was compared by the authors with a biopsy taken from the breast of a man, aged 70 years, who suffered from gynæcomastia following œstrogen therapy for carcinoma of the prostate Albright and his colleagues state that œstrogens produced greater duct hyperplasia and less dense periductal connective tissue than were seen in cases of Klinefelter's syndrome. In one case an assay of urinary œstrogens was performed, and the result was normal. Upon this evidence the authors conclude that the gynæcomastia of Klinefelter's syndrome is not due to "hyperestrinism" They regard testosterone as unlikely to cause gynæcomastia in this syndrome because normal men do not develop this symptom The authors suggest the theory that gynæcomastia in Klinefelter's syndrome is the result of androgen secretion in the absence of "X" hormone They admit that testosterone does not regularly produce gynæcomastia in castrates but believe that a third factor is necessary—namely, that the patient be growing when this hormonal imbalance becomes established.

Some of the conclusions drawn from the excellent descriptive data in this paper merit further discussion In the first place, the important observation of Leydig cell clumping is dismissed as being the result of a relative increase in the prominence of these cells following atrophy of the tubules The authors are in error when they state that "one would expect the interstitial cells to be 40 times as numerous as in the normal testis" One would expect these cells to be 40 times as *concentrated* as in the normal testis—that is, the number in a given microscopic field would increase by 40 It will be necessary to return to this point later

Again the comparison between the breast of a man of 70 years abruptly stimulated by large doses of exogenous œstrogen and that of a young man suffering from gynæcomastia at or soon after puberty is certainly open to question This is especially true when the photomicrographs presented for comparison are examined the similarity between the two specimens is more apparent than the differences In any case, the histology of the breast undergoes considerable change with age, and the sudden stimulation of a breast which has long since ceased to show signs of activity, by enormous doses (by physiological standards) of œstrogen, can hardly be expected to produce changes identical with those seen at puberty under the influence of the same hormone Moreover, it has been shown that the histology of gynæcomastia is not specific for any particular cause, and that in general the appearances resemble those seen after œstrogenic stimulation of the breast (page 23)

One normal urinary œstrogen assay performed some years after the onset of gynæcomastia, by the methods in use in 1942, would add little to the case against œstrogens as the cause of gynæcomastia in Klinefelter's syndrome

The conception of an "X" hormone was purely hypothetical in 1942, and its existence has never been confirmed since that time The idea that such a hormone specifically prevents gynæcomastia during the growth spurt of adolescence seems to attribute an exceptional role to this hypothetical substance

Three years after the paper of Albright and his colleagues, Heller and Nelson[13] offered a new concept of Klinefelter's syndrome Beginning with the view that hyalinization of the basement membrane was the fundamental abnormality in this

condition, they used the device of postulating four basic or constant features of the syndrome without which it could not be diagnosed and a number of variable or inconstant features The constant features are (i) small testes, (ii) hyalinization of the basement membrane of the seminiferous tubules, (iii) azoospermia, and (iv) high urinary gonadotrophin content.

Patients who show these four abnormalities vary from eunuchoid individuals with slight breast development to those who show normal (or nearly normal) male secondary sexual characteristics together with gross gynæcomastia For descriptive purposes three major types are described—namely, eunuchoid, intermediate and normal (Figure 10) The [illegible] d poorly [illegible] absent. [illegible] e sexual development and well-marked gynæcomastia The intermediate type shows some evidence of eunuchoidism, some failure of secondary sexual characteristics, and moderate gynæcomastia

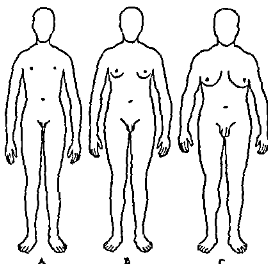


FIGURE 10

The three types of Klinefelter's syndrome according to the concept of Heller and Nelson[8] (A) Marked eunuchoidism without gynæcomastia (B) Moderate development of the secondary sexual characteristics with some gynæcomastia (C) Normal sexual development and marked gynæcomastia

Heller and Nelson at this time envisaged Klinefelter's syndrome as the outcome of a process of hyalinization of the basement membranes which may affect the testis before or during puberty. If this process starts before puberty, eunuchoidism results, if it begins towards the end of puberty, the so-called normal group of Klinefelter's syndrome results Now the normal group is composed of patients who fulfil the requirements of Albright and his colleagues in their original description of the syndrome,[14] while the intermediate and eunuchoid groups are examples of prepubertal testicular failure The only features of the eunuchoid group which could distinguish these patients from other examples of prepubertal testicular failure are the presence of hyalinization of the basement membrane and the state of the Leydig cells. The photomicrographs in the original paper of Heller and Nelson do not illustrate the condition of the basement membrane in the eunuchoid group. On the other hand, they do show an example of the Leydig cells in one patient of this

group, and these cells are described as being in "fair functional state". Whatever their functional state, however, these cells have failed to secrete normal quantities of androgenic hormones, because the patients are eunuchoid and show inadequate development of secondary sexual characteristics.

It seems clear that the changes in the Leydig cells of the eunuchoid group are not sufficiently characteristic to set them apart from other forms of prepubertal failure of the testis While hyalinization of the basement membrane does undoubtedly occur in patients showing eunuchoidism, it remains to be shown that there is in this finding some specificity, ætiological or other, which justifies linking these patients with the classical type of Klinefelter's syndrome. Until the specificity of this hyaline change is established, it seems more satisfactory to group all cases of prepubertal failure of the testis together and to confine the use of the term Klinefelter's syndrome to the so-called normal group, i e, the type of patient described by Albright and his co-workers.

Here the subject of Klinefelter's syndrome remained for more than 10 years, until it was shown by Witschi, Nelson and Segal[4, 16] that some of the patients who were regarded as typical examples of the condition showed female chromatin pattern in the cells of the skin and other tissues These individuals have been called pseudo-males, and they appear in every respect like normal boys throughout childhood At puberty they may notice gynæcomastia, which causes them to seek medical advice, as also may their subsequent infertility The male secondary sexual characteristics show moderate to normal development In one patient described by Witschi and his colleagues,[16] a few seminiferous tubules showed the full histological pattern of spermatogenesis and the chromatin sex was female, this is the nearest approach to complete sex reversal which has yet been described in man *

Witschi and his co-workers[4] have gone so far as to draw an analogy between this state of partial sex reversal and sex reversal in amphibians which can be induced by delay in fertilization of the ovulated egg, which, as a result, shows evidence of degradation Under these conditions the primordial germ cells exhibit degenerative features, multiplying slowly and entering the gonadal folds in small numbers or not at all If no germ cells succeed in entering the gonadal folds, permanent sterility results If, however, a few gonia reach the primordial gonad, the latter develops as a testis regardless of the genetic sex of the host, since the small number of germinal cells (the main inductor of ovarian development) leads to weakening of the cortex, with the result that the medulla gains ascendency over the cortex In the case of minor defects in penetration by the gonia, the competition between cortex and medulla may not be completely resolved, this leads to the production of ovotestes The important factor appears to be the number of germ cells which enter the developing gonad This factor influences the follicular and interstitial cell development, which in turn affects the capacity of these structures to exert their inductive effect upon the genital ducts and external genitalia

It is perhaps too early to press this analogy further, but such a concept more nearly fits these confusing aspects of human sex reversal than other theories so far presented The concept of over-ripeness of the ovum suggests that acquired or environmental factors are responsible for Klinefelter's syndrome rather than hereditary factors. This idea is in accordance with the observation that the syndrome is usually neither familial nor hereditary However, recent evidence suggests that this syndrome is more often inherited than was formerly believed [110]

Among the patients suffering from Klinefelter's syndrome who were examined by Nelson and Boccabella,[17] the ratio of chromosomal females to males was 49 to 13.

* It will be recalled that the germ cells arise outside the developing gonad, probably from the endoderm of the hindgut and that they migrate by amœboid movement to the genital folds, which they proceed to penetrate Witschi's conception of Klinefelter's syndrome is based upon a theory of deficient germ plasm in the zygote resulting from over-ripeness of the ovum before fertilization

If Klinefelter's syndrome is due to some such acquired or environmental cause, this sex difference must be explained, since there is no reason why zygotes of XX genotype should be more frequently affected than those with XY genotype. Presumably the predominance of chromosomal females results from the fact that only the extreme

all degrees of severity When the genotype of the affected zygote is XX and no ... without
ample of
rm cells,
and no
Turner's
syndrome and allied syndromes). With more successful penetration men of low fertility will develop These ideas can be presented in tabular form (after Witschi, Nelson and Segal[4])

TABLE X

Surviving Germ Cells in Gonadal Fold	Genotype of the Affected Zygote	
	XX	XY
None (or very few)	Agonadal women	Pseudofemales
Few	Pseudomales and true hermaphrodites	Men of very low fertility
Moderate	Amenorrhœa and low fertility	Men of low fertility
Normal	Normal women	Normal men

In other words, the result of defective germ cell penetration will depend upon the extent of this deficiency and the genotype of the zygote concerned. Zygotes of XX and of XY genotypes will be affected with equal frequency Some of the patients who suffer from Klinefelter's syndrome with male genetic sex are examples of some acquired but usually unrecognized lesion of the testis which destroys the basement membrane and brings about the same clinical and histological picture

If this concept of Klinefelter's syndrome is correct, there are really three types of this condition

(1) Chromosomal females in whom degeneration of the germ plasm has proceeded to such a stage that this ovarian organizer can no longer induce adequate cortical development in the indifferent gonad, which consequently develops as a testis

(2) Chromosomal males in whom the degeneration of the germ plasm, while not sufficiently severe to produce Turner's syndrome, is yet sufficiently advanced to cause infertility and the features of Klinefelter's syndrome

... pathological process, the nature of which
brane and hence the
lity and the develop-

So far it has not been possible to distinguish these three groups by any clinical or laboratory evidence, and the histological features of the testis appear to be similar in all three groups[18] The patients of Group I will be recognized by the female

TABLE XI
Clinical Features of Six Patients with Klinefelter's Syndrome

Case Number	Height (Inches)	Weight (Pounds)	Span (Inches)	U.S. (Inches)	L.S. (Inches)	Erections	Emissions	Pubic Hair Distribution	Pubic Hair Amount	Axillary Hair	Beard	Temporal Hairline	Voice	Age (Years)
XXXII	69	132	69½	34	35	Normal	Normal	Male	Normal	Normal	Normal	Recession	Broken	19
XXXV	67¾	138	68	33¾	34	Normal	Absent	Male	Scanty	Normal	Normal	Recession	Broken	42
XL	65	130	65½	33	32	Normal	Normal	Male	Normal	Normal	Normal	Recession	Broken	20
XXXVIII	70½	140	68¾	35	35½	Normal	Normal	Male	Normal	Normal	Normal	Recession	Broken	21
XLVI	69	140	69½	34	35	Normal	Normal	Male	Normal	Normal	Normal	Recession	Broken	18
XXVII	72½	154	72½	36	36½	Normal	Normal	Male	Normal	Normal	Normal	Recession	Unbroken	17

chromosomal pattern of their cells, while those of Groups 2 and 3 will be indistinguishable Since the gynæcomastia shows no features peculiar to any one of these groups (e g., age of onset, severity, histology, etc) and since the ... the testis is similar in all three groups

... the chromosomal females it would ... females may be endowed with breast tissue which is inherently more sensitive to hormonal influences than the breast tissue of genetic males.

TABLE XII

Gynæcomastia in Klinefelter's Syndrome

Case Number	Age at Onset of Gynæcomastia	Severity of Gynæcomastia at First Attendance (Grade)	Duration of Gynæcomastia at Follow-up (Years)	Severity of Gynæcomastia at Follow-up	Duration of Gynæcomastia at Operation (Years)
XXXII	14	II	8	II	—
XXXV .	14	III	42	III	—
XL	14	III	—	—	6
XXXVIII	13	III	11	III	—
XLVI	14	II	—	—	6
XXVII .	14	II	4	II	—

Certain workers[108, 109] have described features by which the testes of cases showing female chromosomal sex can be distinguished from those showing male chromosomal sex In the former, tubules are smaller, less regularly spaced, and more severely hyalinized , they are also less likely to show complete spermatogenesis These differences do not however affect the overall picture, which is one of germinal cell failure and clumping of Leydig cells

TABLE XIII

Duration of Gynæcomastia in Klinefelter's Syndrome

Duration of Gynæcomastia (Years)	Patients Submitted to Operation (4)	Patients Not Submitted to Operation (2)
<8	1	2
>8 <20	2	—
>20	1	—

... six cases of Klinefelter's syndrome are shown ... Small testes and gynæcomastia were present ... ame evident during puberty, although it is ... e testes before puberty In spite of the fact that the testes were small, they were larger than the scrotal contents in prepubertal testicular failure, being roughly 1·5 × 1·0 × 0 5 cm It can be seen that eunuchoidism

and decisive evidence of failure of secondary sexual development were absent in these patients (Table XI). Gynæcomastia appeared at about the age of 14 years and reached Grade II or III severity (Table XII). Pain and secretion from the breasts were absent. The breast development soon reached its greatest extent and remained at this level indefinitely; in no case was spontaneous remission seen (Table XIII). None of these patients showed acne; in fact, their skins were remarkably clear. No relevant findings were discovered in the previous health of these patients, and in particular no history suggestive of attacks of orchitis was discovered

cells (Table XV).

TABLE XIV
Laboratory Investigations in Klinefelter's Syndrome

Case Number	17-Ketosteroids (Mg per 24 Hours)	Urinary Gonadotrophins (Mouse Units per 24 Hours)	Semen (Number of Examinations)	Epiphyses (Age at Examination)
XXXII	8 4 9 8	>96 >96	Azoöspermia (5)	Normal for age (19)
XXXV	9 0 4 0 6 3	>48<96 >96 >96	No ejaculate (—)	Epiphyses fused (56)
XL	11 7 12 4 14 2 10 8	>96 >96 >96	Azoospermia (3)	Normal for age (16)
XXXVIII	11 0 12 4	>96 >96	Azoöspermia (3)	Normal for age (14)
XLVI	10 0 12 4 11 2	>96 >96 >96	Azoöspermia (3)	Normal for age (15)
XXVII	8 9 9 4	>96 >96	Azoöspermia (2)	Normal for age (16)

The essential features of Klinefelter's syndrome, as the term is used in this book, are (i) gynæcomastia, (ii) testicular atrophy, (iii) defective spermatogenesis, (iv) raised urinary gonadotrophin, (v) clumping of Leydig cells

These changes may be reduced to a sort of common denominator, because defective spermatogenesis of the degree encountered in Klinefelter's syndrome leads to raised urinary gonadotrophins and to testicular atrophy, since the bulk of the

of Leydig cells

It will be shown elsewhere that this combination of signs is seen in a number of diseases (e g male pseudohermaphroditism, diseases of the spinal cord, leprosy, thyrotoxicosis, etc). It is therefore

A number of workers have described the occurrence of hyperplasia of the interstitial cells of the testis accompanied by defective spermatogenesis. This histological picture is seen as the result of a great variety of morbid and experimental processes

TABLE XV
Testicular Biopsies in Cases of Klinefelter's Syndrome

Case Number	Basement Membrane	Germinal Epithelium	Leydig Cells	
			Distribution	Appearance
XXXII	Hyalinization well marked	Normal spermatogenesis absent Some tubules contain only Sertoli cells	Prominent clumps	Eosinophilic, moderately granular
XXXV	Increased thickness Hyalinization and fibrous thickening well marked	Normal spermatogenesis absent Some tubules contain only Sertoli cells	A few small clumps only	Small, pale, granular
XL	Hyalinization well marked	Normal spermatogenesis absent Some tubules contain only Sertoli cells	Prominent clumps	Eosinophilic, moderately granular
XXXVIII	Hyalinization well marked	Normal spermatogenesis absent Some tubules contain only Sertoli cells	Prominent clumps	Eosinophilic, moderately granular
XLVI	Hyalinization well marked	Normal spermatogenesis absent Some tubules contain only Sertoli cells	Prominent clumps	Eosinophilic, moderately granular
XXVII	Increased thickness Hyalinization well marked	Normal spermatogenesis absent Some tubules contain only Sertoli cells	Prominent clumps	Very eosinophilic and granular

the shrinkage of the tubules lowers the pressure exerted upon the interstitial cells, thereby allowing the nests or groups of these cells to expand He adds that the hyperplasia may be so extreme as to maintain the size of the testis in the face of considerable shrinkage of the tubules

Among the conditions which can give rise to these changes are the following ·

Chronic diseases Pulmonary tuberculosis, cachexia in carcinoma, cardiac failure, chronic nephritis, syphilis, leprosy, untreated advanced diabetes mellitus, pernicious anæmia

Acute illnesses Pneumonia, pulmonary tuberculosis, typhoid fever, polyarthritis.

Miscellaneous. Senile testicular atrophy, undescended testes

Jemerin quotes Kaufman[20] as stating that, in general, in diseases associated

completely destroyed, the hyperplasia is great.

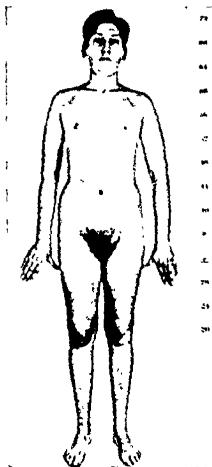


FIGURE 11
Klinefelter's syndrome showing gynæcomastia and small testes without eunuchoidism

intensive or long-lasting to produce at least cessation of spermatogenesis

Félizet and Branca[23] state that in undescended testes interstitial cells are rarely seen before puberty However, in ectopic testes removed after puberty they found atrophy of the seminiferous tubules, accompanied by an increase of the interstitial cells between the tubules, to be the rule

In support of these observations Jemerin[19] has quoted certain experimental observations The testes of dogs were exposed to roentgen irradiation and biopsies taken after each of three successive exposures The testes were finally reduced to about half of normal size After each exposure atrophy of the germinal epithelium was more advanced, and hyperplasia of the interstitial cells became more evident. The authors (Kyrle[22] and Simmonds[24]) concluded that Leydig cell hyperplasia was secondary and compensatory to the parenchymal degeneration This concept was emphasized by the observation that when recovery was permitted after atrophy of the parenchyma had not proceeded too far, regeneration of the epithelium occurred, followed by regression of the interstitial cell hyperplasia

Bouin and Ancel[21] ligated the vas deferens of young rabbits and found that the seminiferous tubules contained no spermatozoa and only a few germinal cells, while there was slight hypertrophy of the interstitial cells When this procedure was performed on one side and the opposite testis removed, after a period of six months the tubules came to contain only Sertoli cells and a few spermatogonia, while the "interstitial gland" was enormously hypertrophied

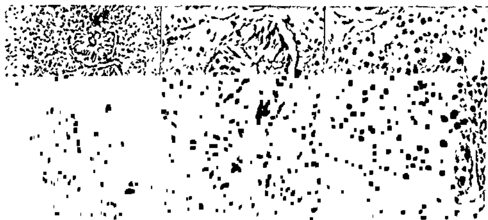


FIGURE 12

The testes in Klinefelter's syndrome (A) Clumps or masses of interstitial cells between atrophic tubules (B) Tubules lined by Sertoli cells Hyalinization of the basement membrane is seen in the tubule on the left (C) A typical clump of interstitial cells

In the regeneration of the testes of dogs exposed to radiation, the parenchyma recovered before the interstitial cell hyperplasia regressed Similarly, in experimental ligation of the vas deferens, defects of spermatogenesis preceded the changes in the Leydig cells Again, some of these causative conditions occasionally produce

cells but never

r these reasons

to those in the

Leydig cells and that the latter were compensatory From his use of the term hyperplasia and from his concept of the pathogenetic basis of the changes in the Leydig cells, it is clear that Jemerin regarded the latter as more than a relative increase in number and prominence

Summarizing these observations, Jemerin states that "in any condition, local, general or experimental, in which cessation of spermatogenic activity and tubular atrophy occur, hyperplasia of the interstitial cells may secondarily ensue The secondary hyperplasia may be so marked as to form almost the entire stroma and even to maintain the size of the testicle despite marked tubular atrophy" He goes on to suggest that the hyperplasia may cause further tubular atrophy by pressure "The primary and initiating factor, however, is the parenchymal destruction"

Among other writers who have reported the association of clumping of Leydig cells in association with destruction of germinal epithelium the following deserve mention:

(1)

(2)

same cha

(3) Hausemann[27] found the same histological changes in cases of tuberculosis, carcinomatosis, syphilis and pernicious anæmia, while Lubarsch[28] and Cordes[29] confirmed these findings in tuberculosis and carcinomatosis.

and the same changes were to be found

(5) In the case of alcoholism (sometimes complicated by cirrhosis, tuberculosis and carcinomatosis) Weichselbaum[32, 33] made similar observations

(6) In acute illnesses Cordes,[29] Bouin and Ancel[21] and Kyrle[22] described the same changes in the testis.

(7) In undescended testes Félizet and Branca,[23] Grynfeldt,[24] Pick,[35] Simmonds,[24] Koch[30] and Kyrle[22] all describe absence of germinal epithelium and Leydig cell hyperplasia

(8) Stroebe,[36] Pick[35] and de Josselin de Jong[37] made similar observations in cases of male pseudohermaphroditism.

Most attempts to explain the ætiology of Klinefelter's syndrome have taken the view that hyalinization of the basement membrane is the essential pathological change The work of Jemerin[19] suggests a mechanism whereby two of the three fundamental features of the syndrome may be linked. Hyalinization interferes

during fixation

On the other hand, the nests of Leydig cells seen in an ordinary histological preparation of the testis should be looked upon as a section of a long strand of such

lestruction of tubules

cation of a stretched

s in place This will

with the result that

cells do not usually show mitoses, while occasional mitotic figures are encountered in the clumps of these cells seen in Klinefelter's syndrome[100] Such mitotic figures were found in all six testicular biopsies of the patients with Klinefelter's syndrome *described in this chapter.*

In order to explore the possibility that the condition of the Leydig cells in Klinefelter's syndrome does not result from an anatomical rearrangement in the testis as the result of destruction of tubules, some estimate of the volume occupied by these cells is *required. Experiments of this nature have been undertaken at* Guy's Hospital. P
of testicular biopsy
thin The areas oc
From the relative weights of the Leydig cell areas and total area it is possible to calculate the relative area occupied by Leydig cells, and from this relative area the proportionate volume of Leydig cells is calculated and expressed as a percentage, *thus* ·

$$\text{Proportionate volume } p = \frac{A_1 \times P_1}{A_1}$$

where A_1 is the area of one field and P_1 is the proportionate area of Leydig cells, i e

$$\frac{\textit{Area of Leydig cells}}{\text{Total area}}$$

This technique is a modification of that described by Eranko[38] and was devised by Dr G Thomas of Guy's Hospital

Table XVI shows the change in volume of the tubules calculated as the cube of the mean tubular diameter The expected proportionate volume of Leydig cells is calculated by assuming that this will increase in proportion to the fall in volume of the tubules. In five cases the observed proportionate volume of Leydig cells exceeds that expected on the basis of these calculations The sixth case is that of a man *aged 56 years who* ... *14 years The* fact that this biops ... ia may explain the fact that clum ... ortunately the exact dimensions of a whole testis in Klinefelter's syndrome have never been reported External measurements of the testis in the scrotum are so inaccurate as to be worthless, but even these rough dimensions suggest that the reduction of testicular volume is greater than the decrease in testicular volume calculated above This is probably ... "blank" ... testis ... ata at ... doubt ... ps of Leydig cells result from relative prominence of the interstitial tissue does not provide an entirely satisfactory explanation for the appearance of these cells in the clumps characteristic of Klinefelter's syndrome and that the possibility of a true increase in the number of Leydig cells must be considered It is to be hoped that careful measurements of testicular volumes in Klinefelter's syndrome will be undertaken in

... t and Branca[23] ... lls appeared in large clumps At puberty the interstitial cells are subjected to gonadotrophic stimulation from the adenohypophysis, and it is probable that the appearance of these cells in clumps represents a response to such stimulation *If we now consider* some of the conditions *which lead to destruction or loss of germinal epithelium* and clumping of Leydig cells, it will be seen that these changes are encountered in genetic females in whom some developmental anomaly has interfered with the development

of tubules, in undescended testes where the tubules themselves have developed

characteristic appearance, which is essentially indistinguishable, regardless of the cause. It seems likely that the appearance of the Leydig cells from causes as diverse as a developmental anomaly on the one hand and a progressive disease of adult life on the other, is more readily understood as the result of hormonal stimulation of these cells than as an architectural change brought about by loss of elasticity or

TABLE XVI

Case Number	Mean Diameters of 100 Tubules (Mm.)			Percentage Distribution of the Three Groups of Tubules			Mean Diameter* (C mm.) × 10⁻⁴	Proportionate Volume of Leydig Cells (Observed)	Expected Proportionate Volume of Leydig Cells
	(a)	(b)	(c)	(a)	(b)	(c)			
XXXII	0·06 × 0·09	0·08 × 0·13	0·15 × 0·14	25	15	60	22	46·1	14
XXXV	0·06 × 0·09	0·09 × 0·14	0·14 × 0·16	59	20	21	10	5·0	30
XL	0·07 × 0·10	0·05 × 0·13	0·14 × 0·16	23	18	59	22	35·0	14
XXXVIII	0·06 × 0·09	0·05 × 0·13	0·14 × 0·15	22	19	59	17	48·0	18
XXVII	0·06 × 0·10	0·07 × 0·13	0·14 × 0·15	19	23	58	22	30·0	14
XLVI	0·06 × 0·09	0·05 × 0·14	0·14 × 0·15	20	28	52	17	39·2	18
10 normal controls	0·14 × 0·17			—	—	—	41	7·5	—

pressure following the destruction of tubules. This is especially so in the case of

that no histological distinction can be drawn between the testes in Klinefelter's syndrome in genetic females and in genetic males.*

It is therefore proposed that the term Klinefelter's syndrome is at the present stage of our knowledge a useful one and is most useful if reserved for a condition involving gynæcomastia, defective spermatogenesis, azoospermia and raised urinary

* [illegible]

gonadotrophins without eunuchoidism but with normally developed male secondary

:

females The tubules show hyalinization of the basement membrane because their development is, as it were, half-hearted. This group can be called true Klinefelter's syndrome, and rarely the full pattern of spermatogenesis is seen in an occasional tubule, pointing to a potentially complete reversal of sex[4] In other cases, in chromosomal males, the testis is affected by some inflammatory or degenerative process the nature of which is obscure and the onset usually latent In either case,

abnormal relationship is clumping of Leydig cells and gynæcomastia The same changes can occur in chromosomal males in whom the germ plasm is deficient (see page 57)

A similar assault on the testis may occur in adult life and change the normal balance between testis and pituitary to an abnormal one, like that seen in Klinefelter's

are consistently associated with gynæcomastia The diseases which have been found to produce this sequence of events are

(1) *Klinefelter's syndrome*
(2) Tumours of the testis
(3) Radiation of the testis
(4) Leprous orchitis
(5) Mumps orchitis
(6) Hyperthyroidism
(7) Male pseudohermaphroditism
(8) Traumatic paraplegia
(9) Friedreich's ataxia
(10) Dystrophia myotonica

The term Klinefelter's syndrome is reserved for those cases with hyalinization of the basement membrane of unknown ætiology, originally described by Albright and his colleagues,[14] including cases of female genotype[4]

Nelson[68] believes that the appearance of the testis in male pseudohermaphroditism is more in favour of the idea that the Leydig cells produce the œstrogens which stimulate and maintain the development of the breasts in this condition He has ... and histological evidence to support this belief and considers that extra-
...unted (because castration causes

Here we have a condition in which
gonadotrophin levels and testicula
syndrome, except that hyalinization of the basement membrane is less evident If the Leydig cells secrete œstrogens in this condition, it is likely that they do so in response to pituitary stimulation since œstrogenic activity first appears at puberty, i e at a time when the pituitary gland is actively secreting gonadotrophic hormones The clumps of Leydig cells may then be under the influence of the interstitial cell-stimulating hormone (ICSH)

If the possibility that the Leydig cells in Klinefelter's syndrome have been stimulated by an increase in the production of ICSH be considered, some explana- [illegible] ...er puberty [illegible] testicular [illegible] ...s that the [illegible] and that castration in this condition causes regression of breast development (see page 99) [101]

If the testis of Klinefelter's syndrome plays some part in the production of gynæcomastia, it seems logical to attribute this action to the Leydig cells, since the Sertoli cells show no evidence of overactivity and in advanced cases become almost obliterated. The cells of Leydig secrete androgens and probably also œstrogens,[48] but until more refined methods are available for estimating urinary œstrogens, the hormone(s) responsible for the gynæcomastia of Klinefelter's syndrome will remain [illegible] syndrome (see page 134)

It is offered as a hypothesis that gonadotrophic stimulation (by ICSH) of the Leydig cells may lead to the development of gynæcomastia Sometimes this stimulation is part of the physiological processes of puberty (subareolar node and [illegible] of or the production of these abnormal quantities of ICSH from the pituitary

Gynæcomastia does not always follow destruction of the germinal epithelium and clumping of Leydig cells Jemerin makes no mention of gynæcomastia in the numerous conditions which he describes as associated with clumping of Leydig cells [illegible] tissue are important in this respect

Recent studies[110] of nuclear sex in Klinefelter's syndrome have produced interesting but confusing data For example, in some cases a disparity between the chromosomal pattern in skin cells and neutrophil leucocytes has been reported Evidence has also been produced for possible translocation of the autosomal elements involved in sex determination, i e chromosomal males could possess less than their share of autosomal sex determining factors (MXY) and chromosomal females could possess more than their share of these factors (MMMXX) These interesting possibilities are purely speculative at present, but are being subjected to further exploration

TUMOURS

Certain tumours of the testis may be associated with gynæcomastia, and although they represent an uncommon cause of this condition the association is important from a diagnostic point of view The following tumours have been reported in association with gynæcomastia (i) chorionepithelioma, (ii) seminoma, (iii) interstitial cell tumour, (iv) Sertoli cell tumour, (v) adreno-cortical rest tumour

Sarcoma of the testis has been reported[18] as a cause of gynæcomastia, but this claim has not been supported by histological data Similarly, one case of a tumour

of the epididymis associated with gynæcomastia was reported by Galliert[50] Such tumours are very rare, and the association with gynæcomastia may have been fortuitous Moreover, in both cases the nature of the tumour must remain in doubt

CHORIONEPITHELIOMA

Chorionepithelioma is more frequently associated with gynæcomastia than other testicular tumours This association was first described by Cooke in 1915, and Gilbert[52] reviewed the literature on the subject Gilbert's paper is based upon 123 cases of choriocarcinoma of the testes, extragenital choriocarcinoma and teratoma of the testis with choriocarcinoma in metastases Bilateral gynæcomastia was present in most cases, and in many a white fluid could be expressed from the nipple On the basis of these cases, Gilbert described a syndrome of choriogenic gynæcomastia, characterized by the following features·

(1) Chorionepithelioma is found in the primary testicular tumour or in its metastases.

(2) Gynæcomastia, usually bilateral, is often the only clinical symptom present.

(3) The areolæ usually show increase in size and/or hyperpigmentation

(4) Milky fluid can be expressed from the nipple, and there may be microscopic evidence of secretory activity in the breast

(5) Chorionic gonadotrophin is present in the urine (sometimes in very large quantities). Œstrone may be present in the urine in abnormal concentrations

(6) The anterior pituitary gland shows the so-called "pregnancy cells".

(7) Hyperplasia of the prostate and seminal vesicles sometimes occur

The term pregnancy cell refers to the hypertrophic basophil cell found in the adenohypophysis during pregnancy

Mechanism of Production of Gynæcomastia

The observations of Gilbert recall the action of chorionic gonadotrophin upon the normal adult testis Maddock and Nelson[53] showed that the hormone produced
[illegible] urinary œstrogens
es gynæcomastia by
Moreover, Shimkin[54]
upon the mammary
ns hormone upon the
breast is indirect

Hyperplasia of Leydig cells in both the [illegible]
chorionepithelioma is reported by Arendt[55] [illegible]
cells in testes of normal size among his own c[illegible]
of spermatogenesis in the unaffected testis The facts at present available do not permit a final statement, but it seems likely that there are two possible explanations for the gynæcomastia seen in chorionepithelioma of the testis—namely, that the tumour secretes chorionic gonadotrophin in such concentration as to stimulate the cells of Leydig to produce an œstrogenic (or possibly an androgenic) hormone, which in turn stimulates the development of breast tissue,[53] or alternatively, that the tumour itself secretes œstrogens, which cause gynæcomastia The correlation between hyperplasia of Leydig cells and a high output of gonadotrophins has not been established in the cases so far reported, although in one series it is likely that such a correlation existed *

Since large doses of chorionic gonadotrophin have been shown to cause damage to the germinal epithelium, it is not unlikely that atrophy of the contralateral testis in patients suffering from chorionepithelioma could result from the production of this hormone by the tumour Until more is known of the action of chorionic

* In a personal communication (1958) Dr R A Moore stated that the data in this series were derived from several sources and that the normal ranges of the gonadotrophin assays mentioned could not be stated with any precision

gonadotrophin upon other endocrine structures such as the adrenal cortex, and until the possibility that these tumours secrete œstrogens has been explored, the mechanism of gynæcomastia in the presence of chorionepithelioma is attributed to the action of chorionic gonadotrophin upon the interstitial cells, which are stimulated to secrete excessive concentrations of œstrogens

Although chorionepithelioma is a rare cause of gynæcomastia, Gordon-Taylor and Till[56] have pointed out that in this group of tumours gynæcomastia indicates a poor prognosis Less often gynæcomastia is an early sign in chorionepithelioma, and urinary assay for chorionic gonadotrophin should be undertaken in cases of gynæcomastia affecting young men between 19 and 40 years of age in whom no other cause of gynæcomastia can be found

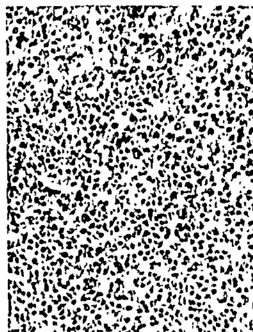


FIGURE 13
Seminoma of the testis in a patient who showed well developed gynæcomastia The uniform cellular appearance of this type of tumour is well shown

SEMINOMA

It is not generally recognized that seminoma may occasionally cause gynæcomastia. The nomenclature of testicular tumours is somewhat confusing, so that it is difficult to assess the incidence of this association from reports in the literature Herzenberg[57] has recorded a case of seminoma with gynæcomastia, and the following patient, who showed gynæcomastia and seminoma, was seen at Guy's Hospital

At the age of 32 years the patient consulted a doctor because of [illegible]
At that time the testes were
of the left testis Biopsy
of operation the gynæcom
showed the microscopic fea
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test before operation was negative

Mechanism of Gynæcomastia

Ferguson and his colleagues[58] showed that a quantitative modification of the Aschheim-Zondek test gave the following results in 117 cases of malignant disease of the testes:

Adult teratoma	50– 500 units
Seminoma	400– 2,000 units
Embryonal carcinoma	2,000–10,000 units
Chorionepithelioma	10,000–40,000 units
Normal male urine	<52 units

Today, however, such diagnostic accuracy is not expected of the Aschheim-Zondek test

Hamburger and Godtfredsen[59] studied the hormonal changes in cases of seminoma of the testis. They concluded that an incre found in 75% of cases of seminoma, and s pituitary origin by means of three observatic

trophin found in the urine of castrates.

In 75% of patients with seminoma urinary gonadotrophin levels between 50 and 400 mouse units were found before surgical or radio-therapeutic treatment. These levels are similar to those found in castrates, but were not found after the removal of the affected testis, even in the presence of metastases Urinary œstrogen levels as measured by bioassay were normal, and urinary androgens were reduced to levels found in normal subjects after the removal of one testis, in the treatment of conditions other than seminoma The authors suggested that the rise in urinary

androgens by the testes

the cause of gynæcomastia in

n reported, and the findings of Hamburger and Godtfredsen relate to cases without gynæcomastia. Seminoma rarely causes gynæcomastia, but the case reported above indicates that breast stimulation may be an early symptom, so that careful and repeated examination

A number of reports

logical identity of the

INTERSTITIAL CELL TUMOURS

cells of the testis, and in 1895 Sacchi[60]

se cells without realizing that he was

of Leydig cells Rowlands, Nicholson and Webster be a case of interstitial cell tumour in which the clinical picture was correlated with a detailed pathological description of

way resemble interstitial

Clinical Picture

Before puberty, interstitial cell tumours cause sexual precocity, as distinct from precocious puberty.[62-65, 49] That is to say, although the penis and secondary

the testes (apart from the tumour) remain

The tumour may be so small as to escape

is difficult, because adrenocortical hyper-

function may produce the same clinical picture. Under these circumstances, when a tumour is felt in one testis, the diagnosis lies between an interstitial cell tumour and an adrenal rest tumour. The distinction in this case can only be made histologically.[66] Sometimes adrenal rest tumours are bilateral, so that both testes are enlarged. In this case the diagnosis lies between precocious puberty of cerebral or idiopathic origin with spermatogenesis and consequent testicular enlargement on the one hand and bilateral adrenal rest tumour on the other.[66] This distinction can be made by testicular biopsy, which will reveal the presence or absence of spermatogenesis.

In adults, interstitial cell tumours, for the most part, present as testicular ... [67] ... id ... ys by modern methods have not been available in the reported cases showing gynæcomastia.[67] It is therefore not possible to draw any final conclusions about the pathogenesis of gynæcomastia in those patients who show precocious puberty and all the expected effects of increased androgen secretion in addition to gynæcomastia. Unfortunately, the cases so far reported have not been accompanied by sufficient evidence to exclude the possibility of adrenal rest tumours.[67]

The pathogenesis of gynæcomastia in patients suffering from interstitial cell tumours leads once more to the disputed origin of testicular œstrogens. In spite of convincing evidence that Sertoli cell tumours in dogs produce œstrogens,[66, 67, 68] there is still much evidence in favour of the Leydig cells as a source of œstrogens. Maddox and Nelson[53] have reported a series of experiments which indicate that ...

contained fully differentiated Leydig cells, and castration led to signs of œstrogen withdrawal and a fall in the level of urinary œstrogens. Nelson concluded that the Leydig cells constituted a more probable source of œstrogens than the Sertoli cells.

These observations are not necessarily mutually exclusive. Perhaps both cells can produce œstrogens. The activity of neoplastic tissue may not provide reliable evidence of the functional capacity of a normal cell or may present a distortion of ...

reconciled in such a way as to explain the source of testicular œstrogens under physiological conditions.

Two examples of feminizing interstitial-cell tumours have been reported in dogs,[70, 71] and in one of these[71] elaborate hormone studies were made. Bioassay ...

authors believe that these findings are in favour of œstrogen secretion by the tumour rather than conversion of androgens to œstrogens.

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Mechanism of Gynæcomastia

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Further studies are required in order to establish the cause of gynæcomastia in seminoma The state of the Leydig cells has not been reported, and the findings of Hamburger and Godtfredsen relate to cases without gynæcomastia Seminoma rarely causes gynæcomastia, but the case reported above indicates that breast stimulation may be an early symptom, so that careful and repeated examination of the testes is required in cases of gynæcomastia in adult men A number of reports of seminoma in the literature are confusing because the histological identity of the tumours reported has not been clarified

INTERSTITIAL CELL TUMOURS

In 1850 Leydig described the interstitial cells of the testis, and in 1895 Sacchi[60] described the first case of a tumour of these cells without realizing that he was presenting the clinical picture of over-activity of Leydig cells Rowlands, Nicholson and Webster[61] were the first authors to describe a case of interstitial cell tumour in

Clinical Picture

Before puberty, interstitial cell tumours cause sexual precocity, as distinct from precocious puberty[62-65, 69] That is to say, although the penis and secondary sexual characteristics are well developed, th
consistent in size with the patient's age[66]
detection, in which case the diagnosis is

In addition, the titre of urinary chorionic gonadotrophin was negative at 750 I.U. per 24 hours and that of F.S.H. was positive at 13 and negative at 52 M.U. per 24 hours.

The affected testis contained a tumour which proved to be of interstitial cell type, while the remainder of the testis showed defective spermatogenesis with few spermatids and no more than occasional spermatozoa.

This case is instructive in several ways. In the first place, urinary œstrogen levels are only slightly raised, although gynæcomastia was recent and pronounced and the state of the germinal epithelium compatible with recent exposure to œstrogens. This must mean that either the secretion of œstrogens was variable or slight increase in urinary levels is compatible with marked gynæcomastia (including pain and secretory activity) and defective spermatogenesis. It is therefore not surprising that high urinary œstrogens have not been reported in essential gynæco-

TABLE XVIII

Hormone Assays in Interstitial Cell Tumour of the Testis

(Case of Herrmann *et alii*[19])

Urinary Steroid	Pre-operative Value per 24 Hours	Post-operative Value per 24 Hours	Normal Range (Male)
Iso-androsterone and dehydro-iso-androsterone	2.2 mg	0.9 mg	—
Androsterone	1.2 mg	1.9 mg	—
Ætiocholanolone	2.9 mg	5.0 mg	—
11-oxy-17-ketosteroids	1.8 mg	1.9 mg	—
Œstriol	15.7 μg	—	<8.2 μg
Œstrone	6.6 μg	—	<7.0 μg
Œstradiol-17β	3.2 μg	—	<1.1 μg

mastia and in conditions associated with clumping of Leydig cells, such a slight increase can be detected only by sensitive methods. It is hard to conceive that the gynæcomastia in this patient could be due to any cause other than the direct action of œstrogens upon the breast. Isolated reports of normal urinary œstrogens in patients suffering from gynæcomastia should not, therefore, be taken to mean that such gynæcomastia cannot be due to excessive secretion of œstrogens.

In the second place, the urinary output of isoandrosterone and dehydroiso-androsterone was high before operation, and an increase in the urinary output of dehydroisoandrosterone has been reported following the administration of œstrogens.[84] Again, the excretion of androsterone and ætiocholanolone (metabolites of testosterone) was low before operation, while that of 11-oxy-17-ketosteroids remained normal, which suggests that the secretion of testosterone was depressed in the presence of the tumour. Modern concepts of the synthesis of hormones suggest a series of equilibria governed by appropriate enzyme systems. The outcome of a given equilibrium is governed, among other factors, by the nature and concentration of the substate and the nature of the enzyme systems at hand. In consequence, a

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hormone

It is now

established that the body can convert androgens to œstrogens.[81, 82, 83] In any case

TABLE XVII

Gynæcomastia and Interstitial Cell Tumours

Author	Age (Years)	Gynæcomastia	Libido	Œstrogens		17-Keto steroids/24 hours	Urinary Gonadotrophins	Clinical Features
				Urine	Tumour			
Hunt and Budd[72]	42	Bilateral	Decreased	—	12 m u /gm	—	Positive Zondek test	—
Huffman[73]	6	Bilateral	—	—	—	—	Negative Friedman test	Precocious genital development
Nation *et alii*[74]	30	Bilateral	—	—	—	—	—	Gynæcomastia present two and a half years after operation
Grabstald *et alii*[75]	32	Bilateral	Decreased	—	—	—	Negative Friedman test	Died of coronary disease one year after diagnosis
Mayers[76]	26	Bilateral	Decreased	4 7 µgm after operation	—	12 3 mg after operation	Prolan A normal	Breasts normal 15 months after operation Libido increased after operation
Christenson and Nettleship[77]	76	Bilateral and transitory	—	—	—	—	—	—
Eisenstadt and Petry[78]	42	Bilateral	Decreased	60 mg * before operation 20 mg after operation	—	13 5 mg (17 OHCS normal)	F S H normal	—
Herrmann *et alii*[79]	20	Bilateral Tender and secretion present	Decreased	Raised	—	See Table XVIII	—	Breasts normal nine months after operation Sperm count and libido normal

* Normal 4-30 mg Reported as mg by Eisenstadt and Petry, presumably a misprint for µgm

In addition, the titre of urinary chorionic gonadotrophin was negative at 750 I U. per 24 hours and that of F S H. was positive at 13 and negative at 52 M.U. per 24 hours

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which suggests that the secretion of testosterone was depressed in the presence of the tumour Modern concepts of the synthesis of hormones suggest a series of equilibria governed by appropriate enzyme systems The outcome of a given equilibrium is governed, among other factors, by the nature and concentration of the substate and the nature of the enzyme systems at hand In consequence, a histological concept has given place to a histochemical one, as the result of which it is now held that the important feature of an endocrine cell, as far as its hormone production is concerned, is not its appearance but its enzyme content It is now established that the body can convert androgens to œstrogens.[81, 82, 83] In any case

there should be no difficulty in accepting the cells of an interstitial cell tumour as the source of œstrogens in the patient described This observation shows that over-activity of Leydig cells, whether neoplastic or hyperplastic, is sometimes associated with gynæcomastia

A patient reported by Cook and his colleagues[85] showed an interstitial cell tumour of the testis without gynæcomastia The urine in this case was studied by chromatographic separation of steroids and was found to contain a high proportion of androsterone and ætiocholanolone but no 3β-hydroxysteroids. This information suggests that the urinary steroids were derived from testosterone rather than from adrenocortical steroids, and hence established the nature of the tumour, which on histological grounds might have been confused with an adrenal rest tumour.

SERTOLI CELL TUMOURS

Sertoli cell tumours might be expected to solve the disputed question of the origin of testicular œstrogens Huggins[86] described a number of examples of this tumour in dogs which showed feminizing changes including gynæcomastia These cases include examples of bilateral tumours and of a tumour in an undescended testis The cells of the tumours contained fat, which distinguished them from germinal cells, and either were minutely tubular or else showed a diffuse, uniform cellularity. The histological appearance of these tumours was quite distinct from that of Leydig cell tumours The tumours were rich in œstrogens

Teilum[87] reported a testicular tumour in a man of 53 years, who presented with gynæcomastia of one year's duration, loss of libido, and impotence. The left testis was large and contained a palpable tumour ; the right was atrophic After removal

why some of the former appeared to cause feminization

Recently, authors have given way before this confusion and prefer to speak of a group of testicular and ovarian tumours as Sertoli-Leydig cell tumours It is at present impossible to simplify matters any further, and it seems unwise to conclude on the basis of these tumours that a given type of cell produces a certain hormone.

LEPROSY

Baptista[40] found gynæcomastia in 8·6% of 842 cases of leprosy Grabstald and Swan[41] have reviewed the literature upon the subject, and in one of the cases they described the patient was submitted to breast biopsy, which showed changes typical of gynæcomastia (see page 22)

The changes in the testis in leprosy occur in three stages,[41] a vascular phase, an interstitial cell phase, and an obliterative phase

Vascular Phase (Acute Leprous Orchitis) —In the vascular phase infiltration of the walls of blood vessels of all sizes by lymphocytes is the earliest change to be seen The wall of the vessel increases in thickness at the expense of the lumen, and lepromata are seen as nodules projecting into the lumen Lymphocytes are also seen in the perivascular and interstitial tissue All stages of spermatogenesis are seen, the basement membrane is normal, and both Sertoli and Leydig cells are histologically intact

Interstitial Cell Phase —The interstitial cell phase, which imperceptibly follows the first, begins as a reactive, obliterative endarteritis Leydig cells are very

prominent, appearing in masses or clumps, and fibrous strands appear in the interstitial tissue. The vessel walls remain thick, but lack the stigmata of inflammation seen in the previous stage. The seminiferous tubules are small, and in most cases they contain only Sertoli cells with occasional spermatogonia, but no spermatids. The basement membrane is thicker than normal, and concentric lamellæ of fibrous tissue are laid down. At the same time the interstitial tissue is seen to contain diffuse collagenous deposits with aggregations of Leydig cells, which are larger, more granular and more eosinophilic than normal. Many Leydig cells contain coarse brown granules.

Obliterative Phase.—The obliterative phase gradually follows, and the vasculature of the testis is further impaired. The outlines of the tubules are finally lost in the progressive fibrosis which follows. Bacilli are usually absent.

[illegible]

were more common in the lepromatous than in the tuberculoid type of leprosy. In patients with testicular atrophy, 17-ketosteroid excretion was normal and the level of urinary gonadotrophins was raised. These observations recall the reciprocity which appears to exist between the Leydig cells and the adrenal cortex (page 54). Cases with adrenal amyloidosis may have shown clumping of Leydig cells with greater regularity because these cells were called upon to compensate for loss of adrenal androgens.

The authors drew attention to the similarity between the final stages of leprous orchitis and Klinefelter's syndrome. Small testes, gynæcomastia, raised urinary gonadotrophins, clumping of Leydig cells and only Sertoli cells within the tubules are common to both conditions. Azoospermia is not mentioned in the cases of leprous orchitis, but in view of the histological appearance of the testis it seems unlikely that the semen could contain mature sperms.

The interest in leprous orchitis lies in the fact that the pathogenesis of the condition has been followed in detail and shown to lead to the same end result as other [illegible]

as in the case of Klinefelter's syndrome (see page 69).

MUMPS ORCHITIS

[illegible]

following bilateral mumps orchitis in a soldier.

Histological findings of the testis in mumps orchitis have been reported infrequently. Recalus[45] described the condition as a parenchymatous sclerosis, and Malasez[46] states that the interstitial tissue is normal but the tubules contain no germinal epithelium. Wesselhoeft,[47] in a study of biopsy specimens taken during incision of the tumour in order to allow expansion of the swollen testis, describes the presence of inflammatory tissue represented by lymphocytes and polymorphonuclear cells. Wesselhoeft produced a similar histological picture by injecting the saliva of patients with mumps into the testes of cats.

However, in those patients who developed gynæcomastia following mumps orchitis an interval of six to 12 months elapsed between the attack of mumps and the first appearance of gynæcomastia We are therefore concerned with the histology of the testis after the acute orchitis has subsided. Howard *et alii*[48] studied the

ents who suffered testicular atrophy

The authors described destruction

leaving only Sertoli cells Some thickening of the basement membrane occurred, and clumping of Leydig cells was prominent Urinary gonadotrophin levels were raised, while 17-ketosteroid excretion was normal So far no report is available of the histology of the testis in patients showing gynæcomastia after mumps orchitis

Gynæcomastia is not a common complication of mumps orchitis. Four patients with bilateral testicular atrophy following mumps orchitis have been seen at Guy's Hospital, and none of these showed gynæcomastia.

The resemblance of the testis affected by mumps orchitis to that of Klinefelter's syndrome is quite striking, and it is tempting to suggest that the same mechanism produces gynæcomastia in the two conditions although proof of this hypothesis is lacking The fact that mumps orchitis does

surprising, since none of the known cases of

symptom

BILATERAL ORCHITIS OF UNKNOWN ÆTIOLOGY

patients suffering from Klinefelter's syndrome is simply one of failure of testicular development, together with the appearance of gynæcomastia at puberty Presumably the same clinical picture could follow any condition which causes destruction of the germinal epithelium In the cases of atrophy of unknown ætiology no retrospective evidence of syphilis, gonorrhœa, tuberculosis or mumps could be found

Three patients who belong to this group were studied at Guy's Hospital Of these, two were typical examples of Klinefelter's syndrome, differing from other examples of this syndrome only in the history of acute orchitis The third patient suffered an attack of pain in the testes with urethral discharge at the age of 14 years This attack lasted three weeks, and the testes remained small thereafter At the age of 22 years the patient noticed swelling of the right breast He had suffered an attack of mumps without orchitis at the age of eight years The patient was of normal stature and showed pubic hair of female distribution , 17-ketosteroid excretion was normal, and the level of urinary gonadotrophins was raised Testicular biopsy (Figure 14) from both testes revealed defective spermatogenesis of such severity as to lead to the appearance of Sertoli cells only within the tubules The basement membrane was normal in most tubules and showed slight hyalinization in the remainder Leydig cells were prominent and occurred in large clumps between the tubules No evidence of mumps, tuberculosis, gonorrhœa or syphilis could be discovered in the history or in the laboratory examinations

This patient differs from those suffering from Klinefelter's syndrome in the

psy and in the

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It is possible that this syndrome of orchitis followed by Klinefelter's syndrome is not rare but has either escaped detection through lack of follow-up studies or has not

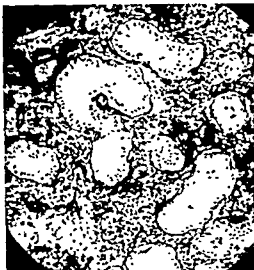


FIGURE 14
The testis in a patient who showed all the features of Klinefelter's syndrome and who gave a history of an attack of orchitis Tubules are lined by Sertoli cells, and some thickening of the basement membrane is evident A group of well developed darkly stained interstitial cells is seen

RADIATION OF THE TESTIS

Woodham[89] reported three cases of gynæcomastia occurring in men who had undergone operations for testicular tumours and thereafter been subjected to deep X-ray therapy The records of these patients have been made available through the kindness of Dr Levitt of St Bartholomew's Hospital

CASE I

On February 13, 1935, at the age of 32 years, the patient underwent left orchidectomy for teratoma

From February 18 to March 26 deep X-ray treatment was given to the whole pelvis, scrotum and right half of the abdomen

On September 3 gynæcomastia affecting the right breast was noticed at a follow-up examination The swelling was painful and had not been present at the previous visit in June

On October 10 bilateral gynæcomastia was discovered

On October 17 both breasts were removed surgically. The pathologist reported the presence of " hyperplasia of the breast tissue, with dilatation of the duct system and increase in the stroma "

However, in those patients who developed gynæcomastia following mumps orchitis an interval of six to 12 months elapsed between the attack of mumps and the first appearance of gynæcomastia We are therefore concerned with the histology of the testis after the acute orchitis has subsided Howard *et alii*[48] studied the [illegible] ents who suffered testicular atrophy [illegible] The authors described destruction [illegible] *leaving only Sertoli cells. Some* thickening of the basement membrane occurred, and clumping of Leydig cells was prominent Urinary gonadotrophin levels were raised, while 17-ketosteroid excretion was normal. So far no report is available of the histology of the testis in patients *showing gynæcomastia after mumps orchitis*

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The resemblance of the testis affected by mumps orchitis to that of Klinefelter's syndrome is quite striking, and it is tempting to suggest that the same mechanism produces gynæcomastia in the two conditions, although proof of this hypothesis is lacking The fact that mumps orchitis does not often produce gynæcomastia is not surprising, since none of the known cases of gynæcomastia invariably produce this symptom

BILATERAL ORCHITIS OF UNKNOWN ÆTIOLOGY

Sometimes a clinical syndrome [illegible]'s syndrome results from orchitis of unknown ætio[illegible] puberty and causes painful swelling of both testes [illegible] The acute stage is followed by testicular atrophy and, after a latent interval, by gynæcomastia *It has often been suggested that certain cases of Klinefelter's syndrome follow some* form of orchitis which may not be recognized [4, 15] Usually the history given by patients suffering from Klinefelter's syndrome is simply one of failure of testicular development, together with the appearance of gynæcomastia at puberty Presumably *the same clinical* picture could follow any condition which causes destruction of the germinal epithelium In the cases of atrophy of unknown ætiology no retrospective evidence of syphilis, gonorrhœa, tuberculosis or mumps could be found

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This patient differs from those suffering from Klinefelter's syndrome in the fact that hyalinization was not a prominent feature of the testicular biopsy and in the history of acute orchitis of unknown cause Whatever the nature of the illness at *the age of 14 years,* this patient is another example of the combination of destruction of the germinal epithelium, clumping of Leydig cells and gynæcomastia

UNDESCENDED TESTES

Undescended testes are rarely associated with gynæcomastia. In a series of more than 400 cases of undescended testes Bishop[99] encountered none with gynæcomastia. Crooke[31] reported the case of a man aged 24 years with a right undescended (inguinal) testis and a small left scrotal testis. The patient suffered from gynæcomastia, he had to shave only twice a week, his voice remained unbroken, and although he was potent, ejaculation had never occurred. Biopsy of the left testis revealed atrophic tubules and "hypertrophy of the interstitial cells". The 17-ketosteroid excretion was 2·3 mg per 24 hours.

In this patient gynæcomastia was probably not specifically related to the presence of one undescended testis but rather to a testicular lesion which produced atrophic tubules in testes of which one happened to be undescended. In the absence of further data it is not possible to regard this as an example of Klinefelter's syndrome, but it seems likely that the gynæcomastia is to be explained by changes in the testis which resemble those found in that syndrome.

CASTRATION

Castration has been given as a cause of gynæcomastia,[91] and although prepubertal testicular failure is sometimes associated with gynæcomastia, the occurrence of gynæcomastia in cases of prepubertal castration is uncertain. Hekmet and Regnant and Wagenseil[92, 93] studied a large group of Turkish eunuchs and found no evidence of gynæcomastia. Most authors agree that castration, whether before puberty or after, does not cause gynæcomastia. None of nine post-pubertal castrates seen at Guy's Hospital showed gynæcomastia.

TRAUMA

Although reports[95, 96, 97, 107] have appeared in the literature of cases in which gynæcomastia has followed traumatic testicular lesions, only one[95] of these reports is sufficiently detailed to be convincing. In this case repeated episodes of testicular injuries led to atrophy of one testis and left the other smaller than normal. Soon after the last of these injuries, at the age of 18 years, gynæcomastia appeared. Presumably the germinal epithelium suffered considerable destruction in this case, and this may have been related to the occurrence of gynæcomastia. Testicular trauma must be regarded as a very rare cause of gynæcomastia, and the mechanism of breast development under such circumstances remains unknown.

UNILATERAL TESTICULAR LESIONS

VARICOCELE

A number of cases are recorded in the literature of gynæcomastia associated with varicocele.[49, 88, 89] Sometimes gynæcomastia follows an operation for varicocele. One patient seen at Guy's Hospital had a small right testis which had been operated upon for varicocele and showed the histological picture of Klinefelter's syndrome, while the left testis was undescended and could be felt in the inguinal canal. The 17-ketosteroid excretion was normal, and the level of urinary gonadotrophins was raised. Gynæcomastia appeared at 20 years of age—two years after the operation for varicocele. The gynæcomastia in this patient was probably due to the same cause as that seen in the patient reported by Crooke[31] (see above), and in both patients it is suggested that the mechanism involved is similar to that which operates in Klinefelter's syndrome. In these two patients we are dealing with one testis like those encountered in Klinefelter's syndrome and another undescended testis in which it seems likely that a similar histological picture would be seen.

The deep X-ray therapy in this case involved anterior and posterior pelvic fields and a loin field without protection of the scrotum. The patient was alive and well in 1955. He had been married one year before the orchidectomy and has since remained potent, but has no children The right testis was soft and atrophic

CASE II

On September 1, 1936, the patient, aged 37 years, was subjected to right orchidectomy for teratoma

On October 13 painful left-sided gynæcomastia was noticed Deep X-ray treatment was begun

On December 12 deep X-ray treatment finished. Throughout this treatment the left breast had grown larger, while the right remained normal The gynæcomastia disappeared during the next four months

On April 15, 1937, the patient was well, and no evidence of gynæcomastia was to be found.

The technique of radiation in this case was the same as that used in the first patient, and again the scrotum was not protected

CASE III

In 1935, at the age of 28 years, the patient underwent right orchidectomy for an undescended testis, which was found to be the site of a seminoma

On March 9, 1937, deep X-ray therapy to the para-aortic glands was begun

On March 23 a mass in the right leg was noticed, and radiation was applied to the leg

On April 6 radiation was again directed at the para-aortic glands

On May 28 deep X-ray therapy was stopped

On June 17 bilateral painful gynæcomastia was noticed

On July 29 the gynæcomastia had quite disappeared

In this case a "bath" of deep X-ray therapy was directed at the para-aortic glands, a

groin

mastia

remained potent but has no children The left testis was described as normal before deep X-ray treatment but is now soft and atrophic During the treatment pubic hair fell out and has remained scanty ever since

COMMENT

The fact that the first and third patients did not notice gynæcomastia before

gynæcomastia after operation but before deep X-ray treatment Unfortunately, further endocrine studies were not possible in these patients, so that the ætiology

with clumping of Leydig cells (see page 69) *

* It is interesting that no cases of gynæcomastia have been reported among the Japanese victims of atomic blasts Colonel V Meneces examined a large number of the survivors and in a personal communication (1954) stated that he had not seen gynæcomastia although testicular atrophy has been reported [114]

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UNILATERAL TESTICULAR ATROPHY

Unilateral testicular atrophy of unknown ætiology is occasionally associated
...rance of both testes in a man, aged
... before the biopsy was taken The
... puberty. The atrophic right testis showed defective spermatogenesis and thickening of the basement membrane, while the left testis was normal clinically and histologically. Urinary gonadotrophin excretion was low. In this patient the gynæcomastia was associated with loss of libido and impotence.

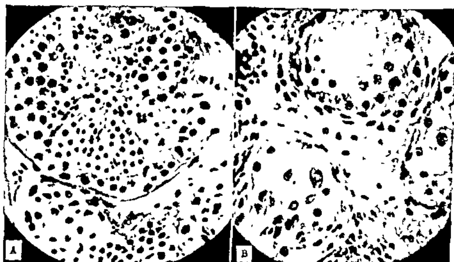


FIGURE 15

The testes in a patient with unilateral testicular atrophy and gynæcomastia (A) The left testis is normal, (B) the right (atrophic) testis shows defective spermatogenesis

Gynæcomastia is difficult to explain in such a patient The explanations suggested in previous pages to explain the occurrence of breast stimulation in bilateral testicular lesions can scarcely apply in such a case

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Special Investigations

Hormone Assays

(a) *Urinary 17-Ketosteroids.*—Urinary 17-ketosteroid levels are raised in most feminizing adrenocortical tumours, but in 40% of those cases in which only one estimation is recorded the level was normal The percentage of 17-ketosteroids which belong to the β-fraction may be [illegible] bove the normal levels of 5% to 18%, reaching 50% of [illegible] This increase in the β-fraction is the basis of th[illegible] fraction and of a method using the Pettenkoffer react[illegible] a number of similar quantitative tests which give positive results when the proportion of dehydroisoandrosterone (the principal β 17-ketosteroid) exceeds 50% of the total 17-ketosteroid output.[3] The β-fraction is chiefly composed of steroids of adrenocortical origin, and this test helps to distinguish adrenocortical from interstitial cell tumours (see page 76).

(b) *Urinary Œstrogens*—The estimation of urinary œstrogen levels is a most valuable diagnostic procedure in adrenocortical tumours. In only one case among 15 in which urinary œstrogen levels are recorded was the result within normal limits (see Table XIX) The principal drawback to urinary œstrogen studies lies in the technical difficulties involved However, chemical methods are now being used more widely, although these procedures are laborious, they are accurate, and it is to be hoped that they will facilitate the diagnosis of feminizing adrenocortical tumours

(c) *Urinary Gonadotrophins*—Estimation of urinary gonadotrophin levels has not been of value either in diagnosis or in elucidating the hormonal changes found in adrenocortical overactivity In some cases the levels are low, the majority are normal, while in a few instances high levels have been found

Semen Examination. Azoöspermia is commonly seen

Testicular Biopsy Diminution in the number of Leydig cells and defective spermatogenesis have been described

X-ray Examination (a) Plain X-ray examination of the abdomen may reveal calcification within the tumour (b) Intravenous pyelography may show displacement of the kidney. (c) Presacral insufflation of air may reveal the outline of the tumour This method can be combined with intravenous pyelography[4]

Diagnosis

Since gynæcomastia is a relatively early symptom of feminizing adrenocortical tumours, it follows that every case of unexplained gynæcomastia deserves investigation to eliminate this possible cause No clinical evidence except abdominal tumour will prove helpful in this investigation, since tumours occur at all ages, and loss of libido and testicular atrophy are inconstant The 17-ketosteroid excretion may be raised, but normal levels do not exclude cortical tumour The logical diagnostic procedure would seem to be estimation of urinary œstrogen levels, but this is still not widely available Only one case of the 15 investigated showed normal levels, and the possibility remains that repeated assays may have revealed raised levels in this case

Presacral air insufflation combined with intravenous pyelography may help to demonstrate the presence of a tumour Any patient who shows gynæcomastia and raised urinary œstrogen levels or raised 17-ketosteroid levels in the absence of testicular tumour should be suspected of adrenocortical disease and treated accordingly

Prognosis

Feminizing adrenocortical tumours are usually malignant, and in four of the 34 recorded cases the condition was inoperable when diagnosed, 18 patients were treated surgically, and more than half of these died within seven years of the onset of

CHAPTER IX

GYNÆCOMASTIA ASSOCIATED WITH DISEASES OF THE ENDOCRINE GLANDS

DISEASES OF THE ADRENAL CORTEX

Overactivity of the adrenal cortex may be due to the presence of a tumour or to hyperplasia of the gland. In men it is not possible to recognize a state of "super-masculinization" due to an excess of androgens, but in certain cases of adreno-cortical overactivity some loss of the features of masculinity is seen together with gynæcomastia [1, 2, 3] This state of affairs is referred to as feminization, and the group of adrenocortical lesions causing it as examples of feminizing tumours or adrenocortical hyperplasia with feminization, as the case may be.

Adrenocortical overactivity is not a common condition, and feminizing adreno-cortical overactivity is of great rarity Wallach *et alii*[4] found 34 examples of feminizing adrenocortical carcinomata (including one of their own) up to 1957, while Bishop[1] found three cases of adrenocortical hyperplasia with feminization

Feminizing Adrenocortical Tumours

[illegible]

does not facilitate early diagnosis of these conditions and does not demand special treatment In the case of adrenocortical tumours it is otherwise Here gynæcomastia may be the first symptom which takes the patient to the doctor, and since these tumours are usually malignant, the only hope of effective treatment lies in early surgical removal The problem is made more difficult by the rarity of adrenocortical tumours as a cause of gynæcomastia In other words, it is necessary to eliminate this [illegible] urgent need for ear[illegible] r of patients will be [illegible]

Clinical Features

Amon[illegible]ant in every case except one,[4, 5] as judged [illegible] the latter is very variable and difficult to [illegible] varied from 5 to 59 years, the patient ag[illegible] patients aged 14 and 15 years are the only adolescents The remaining patients were distributed almost equally between the third, fourth and fifth decades

[illegible]

hypertension are recorded, but other features of Cushing's syndrome are [illegible] in only two cases [4]

removal of the tumour revealed a considerable fall in the excretion of these hormones and a decrease in the extent of the gynæcomastia.[5, 10, 17, 18, 20, 23]

Although the normal adrenal cortex produces small amounts of œstrone, these are insufficient to stimulate the normal male breast. The evidence provided by the recorded cases is overwhelmingly in favour of the view that feminization in these tumours results from the production of excess œstrogens, and no doubt gynæcomastia results from the direct action of these hormones upon the breast.

Tumours of the testis may occur in ectopic adrenal tissue (so-called adrenal rest tumours). Ectopic cortical tissue can occur in the kidney or in the liver, along the path of descent of the testis or within the testis itself. Apart from these sites, adrenocortical tissue may be found almost anywhere within the abdomen. Adrenal rest tumours of the testis may closely resemble interstitial cell tumours under the microscope (page 12). The occurrence of gynæcomastia in association with such tumours is the result of œstrogens secreted by the cells of the tumour and is of the same diagnostic importance as that seen with cortical tumours elsewhere. Ostergaard[10] has reported such a tumour in a man of 28 years who complained of gynæcomastia The right testis was small, and a tumour was felt at the upper pole of the left testis Hormone assays before and after operation gave the following results.

Assay	Before Operation	After Operation
Urinary gonadotrophins	50 mouse units (normal)	50 mouse units (normal)
Urinary œstrogens	200 mouse units (raised)	50 mouse units (normal)
Friedman reaction	Negative	——
Androgens	25 I U (raised)	6 2 I U (normal)

HYPERPLASIA

All that has been said about gynæcomastia in adrenocortical tumours can be repeated in the case of hyperplasia except that hyperplasia is more difficult to demonstrate radiologically Although the number of recorded cases is insufficient to support dogmatic statements, it appears that, apart from the presence of the tumour itself, the clinical picture of hyperplasia is identical with that of tumour, and the mechanism by which the two conditions produce gynæcomastia is the same

It is interesting to notice that patients suffering from female pseudohermaphroditism (due to adrenocortical hyperplasia) show breast development when the cortisone, with which they are commonly treated, is withheld The onset of mammary gland enlargement has been seen in this condition in patients as young as six years of age when cortisone treatment is abruptly suspended for some reason.[88]

STRESS

In rare instances, breast development has been reported following extensive burns, and the sudden onset of lactation occasionally follows exposure to stress[67] Selye explains this interesting observation as the result of the action of hydrocortisone upon the breast Exposure to stress results in an increase in the secretion of glucocorticoids, and Selye[68, 68a, 69] has shown that hydrocortisone given to adrenalectomized-ovariectomized animals treated with small doses of œstradiol, produces considerable stimulation of the mammary gland together with secretory activity.

symptoms. The only patient who could be regarded as showing a benign tumour underwent surgical treatment 16 years after the onset of symptoms and was well one year later.[5]

The prognosis of these tumours is therefore grave, but the disease may run a prolonged course with metastases in the liver, lung and elsewhere. One possible way of improving this state of affairs involves thorough investigation of cases of unexplained gynæcomastia.

TABLE XIX

Urinary Œstrogens in Adrenocortical Tumours

Case Report and Reference	Œstrogen (Bioassay) per 24 Hours	Normal for Patient's Age or Comparison with Normal
Simpson and Joll[7]	3200 M U	Raised
Roholm and Teilum[13]	5000 M U	<20 M U
Hurxthal and Musulin[9]	60 R U	<10 R U
Ostergaard[10]	200 M U	Raised
Scott[12]	5 3 μg (α-œstradiol equivalent)	Normal
Wilkins[13]	5 R U	1 R U
Luft and Sjogren[14]	250 I U	—
Nusimovish[20]	5000 units/litre	—
Pickard *et alii*[20]	160 I U	—
Dohan *et alii*,[17] Case 1	4000 M U	13–44 M U
Dohan *et alii*[17] Case 2	460 M U	13–44 M U
Staubitz *et alii*[18]	3340 I U	25–130 I U
Case record,[19] M G H	1235 μg "œstrogen"	40–80 μg
Higgins *et alii*[20]	2600–6200 μg	Raised
Wallach *et alii*[4]	73–177 μg œstrone (equivalent)	2–29 μg

Pathogenesis

The mechanism by which overactivity of the adrenal cortex produces gynæcomastia seems clear. In all but one of the recorded cases in which urinary œstrogen levels were reported there was a distinct rise in the level of œstrogens excreted. Presumably, adrenocortical overactivity can produce a number of different hormones, some of which may be abnormal (i e not produced by the normal cortex) Increased amounts of œstrone, œstriol, œstradiol and pregnanediol have been found in the urine in two cases,[5, 21] while in one case the tumour itself was found to be rich in progesterone and in equilenin, which is a weak œstrogenic steroid, not previously identified in man.[4] In six cases estimations of urinary œstrogens after surgical

removal of the tumour revealed a considerable fall in the excretion of these hormones and a decrease in the extent of the gynæcomastia.[5, 10, 17, 18, 20, 22]

Although the normal adrenal cortex produces small amounts of œstrone, these are insufficient to stimulate the normal male breast. The evidence provided by the recorded cases is overwhelmingly in favour of the view that feminization in these tumours results from the production of excess œstrogens, and no doubt gynæcomastia results from the direct action of these hormones upon the breast.

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Urinary œstrogens	200 mouse units (raised)	50 mouse units (normal)
Friedman reaction	Negative	—
Androgens	25 I.U. (raised)	6.2 I.U. (normal)

HYPERPLASIA

All that has been said about gynæcomastia in adrenocortical tumours can be repeated in the case of hyperplasia except that hyperplasia is more difficult to demonstrate radiologically. Although the number of recorded cases is insufficient to support dogmatic statements, it appears that, apart from the presence of the tumour itself, the clinical picture of hyperplasia is identical with that of tumour, and the mechanism by which the two conditions produce gynæcomastia is the same.

It is interesting to notice that patients suffering from female pseudo-hermaphroditism (due to adrenocortical hyperplasia) show breast development when the cortisone, with which they are commonly treated, is withheld. The onset of mammary gland enlargement has been seen in this condition in patients as young as six years of age when cortisone treatment is abruptly suspended for some reason.[66]

STRESS

In rare instances, breast development has been reported following extensive burns, and the sudden onset of lactation occasionally follows exposure to stress.[67] Selye explains this interesting observation as the result of the action of hydrocortisone upon the breast. Exposure to stress results in an increase in the secretion of gluco-corticoids, and Selye[68, 68a, 69] has shown that hydrocortisone given to adrenal-ectomized-ovariectomized animals treated with small doses of œstradiol, produces considerable stimulation of the mammary gland together with secretory activity.

DISEASES OF THE THYROID GLAND

HYPERTHYROIDISM

In 1848 Basedow[25] published his famous paper on hyperthyroidism ... described atrophy of the female breast ...

Among the 22 reported cases of ... the majority are either incomplete ... to exclude the possibility of a for ... ... lately, the two conditions have appeared at the same time and have undergone synchronous remissions in such a way as to suggest a more significant association Two patients to be described are exceptional in that they raise the possibility that the enlarged breasts contained active thyroid tissue

Table XX contains some relevant facts about the 22 reported cases, together with three other cases not so far reported and one case studied by the author. It will be seen that most of these cases have not been studied ... detail to help in elucidat... 18 of ... and ...

... Sterling... described a ... mentioned in Table XX ... ffered bilateral ... was followed by ... were given of ... removed at operation

Dr Albright's[31] first patient was ... had suffered from ...

... the patient was given a course of potassium iodide after which the thyrotoxicosis and the gynæcomastia disappeared synchronously within three months

This case illustrates the association of thyrotoxicosis and gynæcomastia which appeared together and disappeared after treatment of the hyperthyroidism These observations suggest that in some way the two conditions were ætiologically associated, but the available data give no hint as to the way in which such an association might be brought about

Dr Albright's ...

TABLE XX

Hyperthyroidism and Gynecomastia

Author	Age at Onset of Hyperthyroidism (Years)	Relation between Onset of Gynecomastia and Hyperthyroidism	Diagnosis of Hyperthyroidism	Gynecomastia	Testes	Sexual Power	Treatment	Follow-up
Van Basedow[33]	37	Gynecomastia followed hyperthyroidism by three months	Clinical	Bilateral	?	?	None	?
Freeman[34]	37	Gynecomastia followed hyperthyroidism by three months	Clinical	Bilateral		—	—	—
Murphy[37]	-	Gynecomastia appeared after onset of hyperthyroidism	Clinical	Left	?	?	Mastectomy and thyroidectomy	Cured
Rernbach[38]	52	Simultaneous	Clinical	Bilateral	Small	Impotence	Thyroidectomy	Cure of both conditions
Besley[38]	12	Simultaneous	Clinical	Bilateral	?	?	?	?
Sterling I[40]	?	Simultaneous	Clinical Associated with diabetes mellitus	Bilateral	?	?	?	?
Sterling II[39]	22	Simultaneous	Clinical	Bilateral	?	?	?	?
Sterling III[39]	30	Simultaneous	Clinical Lipodystrophy	Bilateral	?	?	?	?
Menville I[44]		Simultaneous	Clinical No laboratory data	Bilateral	?	?	Thyroidectomy	Cure of both conditions

TABLE XX—*Continued*

Hyperthyroidism and Gynæcomastia—Continued

Author	Age at Onset of Hyperthyroidism (Years)	Relation between Onset of Gynæcomastia and Hyperthyroidism	Diagnosis of Hyperthyroidism	Gynæcomastia	Testes	Sexual Power	Treatment	Follow-up
Menville II[31]	–	Simultaneous	Clinical No laboratory data	Bilateral	?	?	Thyroidectomy	Cure of both conditions
Wheeler I[32]	42	Gynæcomastia followed hyperthyroidism by two months	Clinical B M R, +59%	Left	Normal	?	Thiouracil	B M R, +2%, cholesterol, 240 mg %; cure of both conditions
Wheeler II[32]	42	Simultaneous	Clinical B M R, +90%	Bilateral	Normal	?	?	?
Fraser[33]	43	Gynæcomastia followed hyperthyroidism by several months	Clinical and laboratory findings typical	Bilateral	Normal	Reduced	Propylthiouracil	Cure of both conditions
Starr I[34]	45	Simultaneous	Clinical B M R, +31%	Bilateral	Atrophy	Normal	Thyroidectomy	Remission of both and later relapse of both
Starr II[34]	28	Gynæcomastia followed hyperthyroidism by 10 months	Clinical B M R, +54%	Right	Normal	Normal	Thyroidectomy	Cure of both conditions
Albright I[35]	45	Simultaneous	Clinical B M R, +38%	Right	Normal	Normal	Potassium iodide	Remission of both conditions
Albright II[35]	29	Hyperthyroidism before gynæcomastia by nine months	Clinical and laboratory	Bilateral	Small	Impotence	Thyroidectomy	Remission of both conditions
Guy's Hospital	56	Simultaneous	Clinical and laboratory	Bilateral	Normal	Impotence	Propylthiouracil	Remission of both conditions

Table XX—*Continued*

Hyperthyroidism and Gynecomastia—Continued

Author	Age at Onset of Hyperthyroidism (Years)	Relation between Onset of Gynecomastia and Hyperthyroidism	Diagnosis of Hyperthyroidism	Gynecomastia	Testes	Sexual Power	Treatment	Follow-up
Rosenthal I[14]	41	Gynecomastia followed hyperthyroidism by six months	Clinical and laboratory	Bilateral	Normal	?	Carbimazole	Remission of both conditions
Rosenthal II[14]	48	Gynecomastia followed hyperthyroidism by seven months	Clinical and laboratory	Bilateral	Normal	?	Carbimazole	Remission of both conditions
Ballinger[15]	27	Gynecomastia present from puberty	Clinical and laboratory	Bilateral	Undescended	Impotence	Thiouracil	No change
Treves[16]	56	?	Clinical and laboratory	Bilateral	?	?	Subtotal thyroidectomy	Remission on both conditions
Berson I[17]	31	Simultaneous	Clinical and laboratory	Bilateral	Normal	Normal	Tapazole and thyroidectomy	Cure of both conditions
Berson II[17]	27	Gynecomastia followed hyperthyroidism by four months	Clinical and laboratory	Bilateral	Normal	Normal	Tapazole and thyroidectomy	Cure of both conditions
Berson III[17]	24	Simultaneous	Clinical and laboratory	Bilateral	Normal	Normal	Tapazole and thyroidectomy	Cure of both conditions
Berson IV[17]	55	Simultaneous	Clinical and laboratory	Right	Normal	Normal	I[131] and tapazole	Cure of both conditions

TABLE XX—*Continued*

Hyperthyroidism and Gynæcomastia—Continued

Author	Age at Onset of Hyperthyroidism (Years)	Relation between Onset of Gynæcomastia and Hyperthyroidism	Diagnosis of Hyperthyroidism	Gynæcomastia	Testes	Sexual Power	Treatment	Follow-up
Menville II[31]	—	Simultaneous	Clinical No laboratory data	Bilateral	?	?	Thyroidectomy	Cure of both conditions
Wheeler I[32]	42	Gynæcomastia followed hyperthyroidism by two months	Clinical B M R, +59%	Left	Normal	?	Thiouracil	B M R, +2%, cholesterol, 240 mg %, cure of both conditions
Wheeler II[32]	42	Simultaneous	Clinical B M R, +90%	Bilateral	Normal	?	?	?
Fraser[33]	43	Gynæcomastia followed hyperthyroidism by several months	Clinical and laboratory findings typical	Bilateral	Normal	Reduced	Propylthiouracil	Cure of both conditions
Starr I[34]	45	Simultaneous	Clinical B M R, +31%	Bilateral	Atrophy	Normal	Thyroidectomy	Remission of both and later relapse of both
Starr II[34]	28	Gynæcomastia followed hyperthyroidism by 10 months	Clinical B M R, +54%	Right	Normal	Normal	Thyroidectomy	Cure of both conditions
Albright I[35]	45	Simultaneous	Clinical B M R, +38%	Right	Normal	Normal	Potassium iodide	Remission of both conditions
Albright II[35]	29	Hyperthyroidism before gynæcomastia by nine months	Clinical and laboratory	Bilateral	Small	Impotence	Thyroidectomy	Remission of both conditions
Guy's Hospital	56	Simultaneous	Clinical and laboratory	Bilateral	Normal	Impotence	Propylthiouracil	Remission of both conditions

6·9 gm per 100 ml ; albumin, 3·6 gm. per 100 ml ; globulin, 3·1 gm per 100 ml , albumin/globulin ratio, 1·16

The pyruvate tolerance test gave the following results · fasting blood pyruvic acid, 1 29 mg per 100 ml , 60-minute blood pyruvic acid, 1·38 mg per 100 ml , 90-minute blood pyruvic acid, 1 1 mg per 100 ml

The normal upper limits are fasting, 1·1 mg ; 60 and 90 minutes, 1·39 mg per 100 ml This test was repeated after 10 days, during which time the patient was given injections of vitamin B (see below) The results then were : fasting blood pyruvic acid, 1·0 mg per 100 ml , 60-minute blood pyruvic acid, 1·37 mg per 100 ml ; 90-minute blood pyruvic acid, 1·11 mg. per 100 ml

Before antithyroid drugs were administered, the patient received a course of intramuscular injections of vitamin B, *the daily dose being thiamine 10 mg , riboflavine 4 mg , pyridoxine 4 mg ,* and nicotinamide 40 mg (given in the form of Becosyn, 2 c c daily)



FIGURE 16

Gynæcomastia in a patient suffering from hyperthyroidism (*a*) The breasts before treatment (*b*) The breasts after one month's treatment with propylthiouracil (*c*) Testis normal for the patient's age

At the end of one week no change was seen in the breasts Propylthiouracil was then administered in doses of 400 mg daily Three weeks later the patient had gained 12 pounds weight and clinical evidence of hyperthyroidism had disappeared Gynæcomastia became much less pronounced, and during this treatment the patient noticed that his beard stopped growing for two weeks Thereafter it began to grow, and libido and potency returned. The basal metabolic rate was −2% A maintenance dose of propylthiouracil (200 mg daily) was prescribed

After six weeks of treatment the patient stopped taking the tablets and noticed that libido and potency declined, while the breasts became tender He resumed the tablets, and these changes were reversed During the next nine months he took the tablets and remained well *the gynæcomastia did not return*

This patient suffered a severe and acute form of thyrotoxicosis which was complicated by gynæcomastia, loss of libido and impotence These complications appeared soon after th
successfully treated
tests, and scanning of t
tion of 70 μc. of I[131] ir
tissue Liver functior
liver as a factor in the
after treatment with vitamin B indicated that relative avitaminosis produced by the metabolic stimulation of hyperthyroidism was not a factor in causing breast stimulation The result of testicular biopsy was normal for the patient's age and excluded any possibility of the mechanism suggested in the patient reported by Dr Albright

The only positive finding of any significance in this patient was a high urinary œstrogen level. Although the levels recorded in this patient are higher than those

which are usually present, except for an occasional pigment granule resembling lipofuchsin This is considered to be hyperplasia of the Leydig cells "

The patient received a course of Lugol's iodine, followed five months later by subtotal thyroidectomy One month after operation the thyrotoxicosis had disappeared and the breasts were normal, the testes had reached normal size, and libido and potency had returned

In this patient
appears to be more tha
(ii) small testes, (iii)
changes are those of
distinguished by the a ... ty and
by the absence of the ... The
occurrence of destruct ... g cells
are further points in ... ion is
reminiscent of the case of leprous orchitis, in which the changes of Klinefelter's
... basement membrane but by
It is not clear how hyper-
appearance of gynæcomastia
following successful treatment of the thyrotoxicosis suggests that this disease was directly or indirectly responsible for stimulation of the breasts; and in view of the resemblance which this case bears to cases of Klinefelter's syndrome, it seems likely that the gynæcomastia is the result of a similar mechanism.

The Guy's Hospital patient was rather different

... l June, 1954, when he complained of fulness
in weight during the previous six months
iving up smoking Three months later, in
was beating rapidly, and although at the
At this stage his weight was 98 pounds.

The patient was ordered to bed for one month, during which time he suffered attacks of palpitation which were rapid, and at times irregular He also complained of trembling of the hands and vivid, frightening nightmares *During this period in bed he noticed that his* breasts were swollen and tender On several occasions they discharged a thin whitish fluid He was allowed up after one month in bed and three months later he complained of sudden,
complete impotence and loss of libido
auricular fibrillation with a pulse rate of
of mercury Œdema was absent The a
six inches from the midline, and an apic
was not enlarged, and exophthalmos was
tremor *and warm moist skin were found*
The genital organs and secondary sexual
tests were performed

(1) Thyroid function The basal metabol
was 105 mg per 100 ml A radioactive iodi
plasma protein-bound activity was 0 89% of
limit of normal was 0 4%), (*b*) scanning of t
gland showed a high uptake of I^{131}, no retros
protein-bound iodine was 0 5 µg per 100 ml

(2) Hormone assays The 17-ketosteroid excretion was 12 3, 13 0, 11 0 and 10 9 mg per 24 hours The urinary gonadotrophins were $>12<16$, $>16<24$ and $>12<16$ mouse units per 24 hours *The urinary œstrogens were* œstrone 15 µg per 24 hours, œstradiol 2 µg per 24 hours, œstriol 31 5 µg per 24 hours

(3) Testicular biopsy In the tubules the basement membrane was normal The germinal epithelium of most tubules showed normal spermatogenesis In a few tubules spermatogenesis was arrested at the stage of primary spermatocytes, *and in a few cases only Sertoli cells were seen*

In the interstitial tissue the Leydig cells appeared normal, and a count of these cells was nine per tubule (normal) (see page 18)

serum protein, 6 1 gm per 100 ml , albumin,
00 ml , albumin/globulin ratio, 1 1 , thymol
ve , colloidal gold reaction, negative serum
th later the direct Van den Bergh reaction was
g per 100 ml , the thymol turbidity and thymol
negative Other values were serum protein,

above, has been discredited by Simpson,[37] who regards this paradox as invariably resulting from carcinoma of the thyroid

These observations lend no support to the suggestion that gynæcomastia may develop in association with hyperthyroidism as the result of hyperplasia of thyroid tissue within the breast. Moreover, in neither the case of Murphy[27] nor in that of Sterling[30] was histological evidence given of the nature of the breast tissue.

HYPOTHYROIDISM

Menville[31] and Wheeler[32] each referred to the occurrence of gynæcomastia associated with hypothyroidism, and Marine[33] has stated that "impotence, loss of libido, testicular atrophy and gynæcomastia are common in myxœdema". None of these authors has supported his claims with accurate clinical and laboratory data. While impotence and loss of libido are not infrequently encountered in hypothyroidism, gynæcomastia is not common. Among 18 men with myxœdema, proved by clinical and laboratory data, at Guy's Hospital, gynæcomastia was not encountered Until further positive evidence to the contrary is obtained, it seems more prudent to regard the association of hypothyroidism and gynæcomastia as fortuitous.

DISEASES OF THE PITUITARY GLAND

ACROMEGALY

Roth[40] described hypertrophy of the left breast with secretory activity in a man suffering from acromegaly The breast showed histological features typical of gynæcomastia (see page 22) In women, acromegaly may be associated with persistent lactation,[41] and it has been suggested that certain eosinophil adenomata may produce excessive quantities of prolactin as well as growth hormone The association of acromegaly and gynæcomastia is probably very rare It is not mentioned by Davidoff,[42] who made an exhaustive study of 100 cases of the disease Until detailed investigations have been reported it will not be possible to indicate the mechanism by which acromegaly causes gynæcomastia

CHROMOPHOBE ADENOMA

Three cases of gynæcomastia associated with chromophobe adenoma have been described

Hanel[43] reported the case of a man with enlarged breasts showing secretory activity at the age of 21 years The patient later became the father of two children and died at 43 years, a chromophobe adenoma was found at autopsy

Moehling[44] reported the case of a man of 52 years who complained of impotence and gynæcomastia for two years The testes were small and pubic hair of female distribution At operation a chromophobe adenoma was found

McCullagh and his colleagues[45] reported gynæcomastia with secretory activity in an adult male who showed an enlarged pituitary fossa without change in fields of vision Sexual activity had always been below normal, although this improved considerably after treatment with testosterone Urinary 17-ketosteroid, gonadotrophin and œstrogen levels were all within normal limits, and a semi-quantitative assay of prolactin was performed upon the urine, this gave normal values, although ageing of the specimens may have occurred The breasts were surgically removed and showed the histological features of gynæcomastia (see page 22), while testicular biopsy (taken after deep irradiation of the pituitary and treatment with testosterone) showed normal spermatogenesis and fewer than normal Leydig cells

It is not possible to explain the pathogenesis of gynæcomastia in this patient The histological appearance of the breasts suggests œstrogen stimulation, and yet no evidence of a testicular or adrenal source of excessive œstrogen secretion could be found, and the urinary œstrogen levels were within normal limits Excessive secretion of prolactin by the pituitary gland is conceivable, but this hormone requires

found in normal ... however, ... years than in a younger ... these œstrogens is uncertain

The abrupt onset of ... and the recu... features of th... a situation in... which is ...

... patients of Rosenthal and Lees[74] were studied from a different point of view The authors were interested in the state of adrenocortical function in patients suffering from hyperthyroidism Although the excretion of 17-ketosteroids[75, 76] 17-hydroxycorticosteroids[77, 78, 79] and ... is usually ... st... ra... ... levels and normal ... showed ... both patients ... levels of 1... In one of ... within nor... function.

These findings were interpreted by ...

... many ca... ... account for the high urinary œstrogen levels in the Guy s Hospital case, and adrenocortical œstrogens may be the cause of gynæcomastia associated with hyperthyroidism This explanation will not account for the findings in Dr Albright's second patient

Ectopic Thyroid Tissue

Although a number of authors have stated that ectopic thyroid tissue can occur in many parts of the body, Nicholson[36] has discussed this subject ... and considers that " thyroid tissue can occur in ... foramen caecum of the tongue and the arch of th... glossal duct or lateral thereto as aberrant masses ... tions—usually in the middle of a line joining the ... the clavicle ". He claims that thyroid tissue does not occur elsewhere as a result of embryological misplacement

In addition, thyroid tissue may occur in the ovary as part of a teratoma, while some authors[38] describe the condition of "*goitre plongeant*" in which the gland may appear as far down the ... In one recor... myxœdema,

The exis... benign metastases , which were said to account for the occurrence of thyroid tissue in parts of the body other than those mentioned

* In the case of hyperthyroidism, however, the gynæcomastia appears at the height of the disease and disappears during treatment in the case of malnutrition gynæcomastia appears during refeeding (see page 113)

biopsy of these glands was not performed. On histological examination the gonads are shown to be composed of tubules devoid of germinal epithelium The tubules contain only Sertoli cells, and the basement membrane may be normal or in some tubules it shows hyaline changes Leydig cells are abundant and appear in clumps[48-55] Urinary gonadotrophin levels are considerably raised, and 17-ketosteroid excretion is within the normal range for adults of either sex. Vaginal smear examination indicates œstrogenic stimulation.

Castration in this condition may lead to the occurrence of hot flushes, some atrophy of the breast tissue and anœstrus vaginal smear.[48, 71] In a case described by Wilkins,[71] castration led to the disappearance of œstrogens from the urine (as measured by the Kober reaction). Male pseudohermaphroditism shows a strong familial tendency; for example, Schneider[72] described six cases in three generations of one family. These factors indicate that the testes in this condition are producing œstrogens, and it seems likely that these hormones are responsible for the breast development, especially since castration leads to some regression of the gynæcomastia The testes resemble the testes in Klinefelter's syndrome except that hyalinization of the basement membrane is less evident These observations suggest that the factors responsible for the occurrence of male pseudohermaphroditism interfere with

another example of gynæcomastia associated with clumping of Leydig cells, and it seems probable that the breast development is due to the same mechanism as that

TRANSVESTISM

Transvestism is a condition which has recently excited a great deal of popular interest as the result of articles appearing in newspapers The term is loosely applied to a heterogeneous group of patients who suffer from an overwhelming desire to wear clothes appropriate to the opposite sex. Among men affected in this way, overt homosexual tendencies are usually absent, and in many cases this strange urge goes beyond the desire to assume feminine clothing to a desire to acquire the physical attributes of woman Most of those affected believe that they are in fact women in whom some developmental aberration has robbed them of their rightful physical heritage, and they point to subtle behaviour patterns which they claim support this view For example, some are said to have preferred dolls to the usual toys appropriate to their apparent sex, this preference may appear at the early age of two years Others follow the hobbies and interests of girls during their childhood and adolescent years

In Hamburger's[57] first paper on this subject a patient is mentioned with testicular atrophy and gynæcomastia, but no further details are given Among the Guy's Hospital cases of Klinefelter's syndrome three patients complained of transvestite desires

unfortun

Still[58] ha

vestism Of the three patients seen at Guy's Hospital, two have received androgen therapy and psychotherapy, which, so far from decreasing their desire to "become women", have confirmed the patients in the unshakeable conviction that they are in reality women Both have (in accordance with this belief) refused operative treatment for the gynæcomastia and have stated their intentions of undertaking any measures which may assist their "real sex" to emerge.

the synergistic activity of œstrogens before it causes stimulation of the breast, and bioassay of prolactin did not indicate excessive quantities of this hormone Treatment with testosterone produced no definite change in the state of the breasts.

HYPOPITUITARISM

Failure of the pituitary gland involving one or more of its trophic functions is not associated with gynæcomastia. It is, moreover, highly probable that gynæcomastia does not occur in the absence of adenohypophysial function, so that, in advanced failure of the gland, gynæcomastia would not be expected. A patient reported by Gibson[46] is stated to have shown gynæcomastia and hypopituitarism, but no evidence is given to support the diagnosis of hypopituitarism

DISORDERS OF SEX

HERMAPHRODITISM

[illegible] show evidence [illegible] hermaphrodites, [illegible] a discrepancy between the sex of the gonads and the apparent sex of the individual concerned This simple classification is still convenient, although recent advances in the genetics of sex determination threaten to supplant this scheme by a more complex system

True Hermaphroditism

True hermaphroditism is rare, and our knowledge of the way in which it is brought about is still incomplete However, in some cases one half of the body is masculine and includes a testis, while the other half is feminine and the gonad is an ovary, the breast on the feminine side of the body is well developed in contrast to its fellow on the other side Such a case was described by Brachetto-Brian and his colleagues [47] Although it would not be correct to refer to the breast development on the female side of the body as gynæcomastia, nevertheless this occurrence is of considerable theoretical interest Whatever hormonal influence has stimulated the development of the breast on the female side of the body, the same hormones must also have reached the other breast in the same concentration and at the same time Presumably, some property of one breast must cause it to respond to hormonal influences which are without effect upon the other breast This situation defies further explanation at [illegible]

Pseudohermaphroditism

Individuals who possess testes, but who show some of the primary and secondary sexual characteristics of woman, are referred to as male pseudohermaphrodites. A great variety of "types" of male pseudohermaphroditism have been described, but one distinctive group, referred to as the Goldberg-Maxwell[48] syndrome, is of interest in connection with gynæcomastia In this condition the body is essentially feminine in appearance and the breasts are normal, although in some cases small nipples and areolæ are seen Pubic and axillary hair fails to develop,* and primary amenorrhœa occurs The vagina ends blindly below a vestigial uterus, and the gonads so closely resemble normal ovaries that the condition has been overlooked when

* The presence of pubic and axillary hair follicles has been demonstrated by biopsy but these structures do not respond to therapeutic doses of testosterone suggesting an inherent insensitivity to androgens Perhaps the response of other tissues, including the breast, to hormones may be atypical in this condition

DIABETES MELLITUS

Although the association of gynæcomastia and diabetes mellitus is mentioned by Wheeler and his colleagues,[31] there is no evidence that such an occurrence is more than a coincidence. Pelner and Waldman[73] described gynæcomastia as a complication of what they called "liver dysfunction diabetes", but in their two patients the associated liver failure was almost certainly responsible for the gynæcomastia (see page 104).

CUSHING'S SYNDROME

essentially metabolic changes of Cushing's syndrome.

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The third patient has submitted to plastic surgery to the breasts and bitterly regrets this step. He has served a sentence for homosexual offences, and neither androgen therapy nor psychoanalytical treatment has altered his desire to become a woman.

MISCELLANEOUS

PROSTATECTOMY

Gynæcomastia has been reported following the operation of prostatectomy. Cheatle and Cutler[59] regard this association as " not infrequent ", and Mann[60] reported the occurrence of bilateral gynæcomastia 11 months after prostatectomy in a man aged 70 years Kondolean[61] described gynæcomastia in two men aged 70 years who had undergone prostatectomy. The first suffered painless bilateral enlargement of the breasts one month after operation, and this disappeared within a year. The second reported swelling of the right breast three months after prostatectomy; this was followed by enlargement of the left breast one month later

Oppenheimer[62] reported gynæcomastia three months after enucleation of an adenoma of the prostate in a man of 64 years, the operation was straightforward and free of post-operative complications. The same author described bilateral gynæcomastia following sphincterotomy of the bladder in a man of 45 years. Swelling of the testes is not mentioned, and no investigations are reported.

In the absence of further clinical and laboratory data these observations are difficult to explain At the age of 60 years or more the occurrence of involutional

mmon than is

nples of the

the bladder

or whether the operation has precipitated the appearance of gynæcomastia, cannot at present be stated

Kuntz[63]

the effect of

the following

after the oth

ligated and cut, destruction of the germinal epithelium and hypertrophy of the Leydig cells occurs (iii) The characteristic feature of the destruction of the germinal epithelium under these conditions is the wholesale sloughing of spermatids and spermatocytes before they undergo necrosis

However, in man removal of one testis and ligation of the opposite vas is performed in the treatment of tubercu

encountered as a result of this operation

the small number of

the involutional type

by operation on the

prostate

ALBRIGHT'S SYNDROME

Polyostotic fibrous dysplasia (Albright's syndrome) was first described by Albright and his colleagues[64, 65] in 1937, although they referred to cases described in earlier papers The condition is characterized by bone cysts, skin pigmentation and, in the female, precocious puberty Before 1937 four males affected by this

neither did a boy described

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whom gynæcomastia

uite normal in other

males affected by Albright's syndrome Neither of the patients reported with

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CHAPTER X

GYNÆCOMASTIA ASSOCIATED WITH DISEASES OF THE LIVER

In 1926 Silvestrini[1, 2] described gynæcomastia as a complication of cirrhosis of the liver and attributed its occurrence to an imbalance among the endocrine glands. In 1937 Dingemanse and Laquer[3] injected œstrogens into mice and could recover these hormones from neither urine nor fæces nor carcass, which suggested that œstrogens were destroyed in the body. In the search which followed for the site of this destruction it was discovered that intraperitoneal injections of œstradiol were

resided in the liver cells and not in the reticulo-endothelial cells.

These discoveries were supported by a number of experiments, in which pellets

ormone was

œstrogenic

in the vaginal epithelium

These experiments were taken to indicate that the liver is capable of inactivating natural and synthetic œstrogens The mechanism of this inactivation was studied by shaking various œstrogens with liver pulp *in vitro* Such experiments showed

that biliary excretion of œstrogens was important, but Morrione[15] showed that inactivation by liver cells was more important than biliary excretion Finally, the technique of splenic implantation was extended to show that the liver required thiamine and riboflavine in order to inactivate œstrogens[10, 11, 12]

These observations provided a possible explanation for a number of symptoms seen in liver disease, includi - the breasts in women, and loss and gynæcomastia in men In r in both sexes and may be attributable to excess of circulating œstrogens * Lloyd and Williams[16] undertook an extensive study of the endocrine glands of 71 patients suffering from cirrhosis Among the 55 males they found that loss of libido and loss of potency were almost universal, *while 42% showed gynæcomastia* *Loss* of axillary hair was seen in 92% and testicular atrophy in 76%, 17-ketosteroid

absence of spermatogenesis

It is tempting to suggest that liver failure interferes with the capacity of the liver to inactivate œstrogens secreted by the testis and perhaps by the adrenal cortex, and that the consequent increase in circulating levels of free œstrogens causes stimula-

In addition, œstrogens

of axillary

depressing

effect of œstrogens upon the release o
and the low 17-ketosteroid levels may
possible explanation of the endocrine
when Glass and his colleagues[37] demonstrated an increase in free œstrogens in the urine of cirrhotic patients

Morrione[15] showed that the testicular atrophy seen in cirrhosis was regularly associated with destruction of the germinal epithelium, which in some cases leaves only Sertoli cells within the tubules Morrione further showed in mice that liver cell damage, caused by carbon tetrachloride, enabled exogenous œstrogens to produce germinal epithelial damage in smaller doses than in normal controls.

Infective hepatitis also causes destruction of the germinal epithelium Rather[17] studied testicular biopsies taken during the active stage of this disease, the criteria of activity being those established by Moon,[18] which include disintegration of liver cells, the presence of Mallory bodies and proliferation of bile ducts During this phase of the disease the germinal epithelium shows changes in spermatogonia and spermatocytes before any change is seen in spermatids or spermatozoa With the exception of radiation of the testis by deep X-rays, this is the only condition in which destruction of the germinal cells occurs in this order rather than in order of maturity of the cells, spermatozoa being most vulnerable.[17] Rather concluded that, although destruction of the germinal epithelium does occur during the active stage of infective hepatitis, it is not complete and is reversible

is less frequent than testicular atrophy, although either may occur without the other.

gynæcomastia

Bernstein[20] described unilateral gynæcomastia in a boy, aged 17 years, who suffered from primary liver cell carcinoma The whole illness lasted 18 months, and gynæcomastia was seen during the last year Histologically the tumour proved to be a primary carcinoma without cirrhosis, and liver function tests indicated a severe impairment Klatskin and Rappaport[21] d… …ients suffering from homologous serum jaundice … each case the patient recovered, and gynæcom… …was fading

It is apparent that a severe degree of liver cell damage can lead to gynæcomastia, impotence and testicular atrophy, and that these symptoms probably result from the effects of œstrogens on the breast and testes Although it has been claimed that the urine contains an excess of unconjugated œstrogens, the methods used in these assays are scarcely accurate in measuring such small concentrations of œstrogens, and some workers have failed to recover excess of unconjugated œstrogens from the urine in cirrhosis The final proof of this hypothesis awaits the development of a more sensitive method of assaying urinary œstrogens

So far we have considered ... gynæcomastia occurs ... level of nutrition Th... ... Chapter XI.

Recent studies[26] of autopsy material indicate that a high percentage of males dying with cirrhosis of the liver show the effects of excess œstrogen In 11 out of 13 testes studied, some thickening of the basement ... of 11 showed hydropic changes in the cytoplas... these changes are believed to result from ... evide... ... ges in the epi- ... These findings ... under the age of 50 years, when such changes are not normally found Hyperplasia of the basoph... ... hypophysis[32] and a ... these changes are ...

... the adrenal cortex remain active ... periods than normal because the liver cells are unable to conjugate these substances and render them inert Failure to detect higher than normal concentrations of free œstrogens in the urine of males suffering from liver cell failure is attributed to technical limitations inherent in present ... this ...

... gated and so continue to act upon the ... One can only conclude that the balance of production and inactivation of steroid hormones is disturbed in liver failure in such a way as to favour excessive œstrogen activity

Ulcerative Colitis

One example of gynæcomastia associated with ... as appeared in the ... ative colitis, ... and finally ... appearance ... ly, both breasts were affected and the patient's condition deteriorated to such an extent that colectomy was performed ... biopsy at this time showed " ... operation of colectomy ... disappeared It is kno... ... velopment of cirrhosis of the liver,[23, ...] and in the absence of further examples of gynæcomastia in association with ulcerative colitis it may be suggested, as a hypothesis, that gynæcomastia under these circumstances is the result of liver cell damage

Hæmochromatosis

If liver cell damage is the cause of gynæcomastia in cirrhosis of the liver, it would be expected that any disease which caused sufficient liver cell failure would cause gynæcomastia This is true of acute infective hepatitis, cardiac cirrhosis and carcinoma However, hæmochromatosis does not appear to cause gynæcomastia Neither Sheldon[34, 35] nor Lawrence,[36] both of whom have studied this disease extensively, has encountered gynæcomastia as a complication of hæmochromatosis

In order to explore this paradox further, two patients suffering from hæmochromatosis were studied at Guy's Hospital, and autopsy material from a third was obtained

CASE I The ... and darkening o... discoloration, esp...

TABLE XXI

Special Investigations in Hæmochromatosis

Test	Case I	Case II	Case III
Serum protein (gm /100 ml)	8·1	6 3	6 8
Albumin content (gm /100 ml)	4·6	3·4	2 9
Globulin content (gm /100 ml)	3 5	2 9	3 9
A/G ratio	1·3/1	1 2/1	0 75/1
Thymol turbidity	Negative	Negative	+ (10 units)
Thymol flocculation	Negative	Negative	+ + + +
Colloid gold reaction	Negative	Negative	+ + + +
Serum bilirubin content (mg / 100 ml)	0 2	0 25	1 75
Liver biopsy	Hæmochromatosis	Hæmochromatosis	Hæmochromatosis (autopsy)
Serum iron (μg /100 ml)	244	272	—
Unsaturated iron-binding capacity	Nil (2 estimations)	Nil (3 estimations)	—
Serum sodium, potassium and chloride contents	Normal	Normal	—
Glucose tolerance test	Normal	Normal	Normal
Basal metabolic rate	+2%	− 3%	—
Serum protein-bound iodine (μgm /100 ml)	Zero	2 0	—
17 Ketosteroids (mg /24 hours)	4 9 13 0	9 3, 8 2 7 8, 13 0	—
Urinary gonadotrophins (mouse units/24 hours)	<6 <6 <6	>6<12 <6 <6	—
Robinson-Kepler-Power test	Normal response (part I), 2 tests	Normal response (part I), 2 tests	—
Urinary œstrogens (μg /24 hours)			
Œstrone	5 6	2 2	—
Œstradiol	0 5	<0 2	—
Œstriol	>45	40	—
Semen	Azoöspermia (3)	Azoöspermia (3)	—
Thorn test*			
17-Ketosteroids	Normal rise	Normal rise	—
Eosinophils	Normal fall	Normal fall	—
Adrenaline test	No response	No response	—

* See Tables XXII and XXIII

Recent studies[26] of autopsy material indicate that a high percentage of males *dying with cirrhosis of the liver show the effects of excess œstrogen* In 11 out of

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findings

are reported in men dying under the age of 50 years, when such changes are not normally found Hyperplasia of the basophil cells of the adenohypophysis[32] and a narrow nodular adrenal cortex[33] are also found in cases of cirrhosis ; these changes are also thought to be due to œstrogen stimulation [26] There is, therefore, considerable circumstantial evidence to indicate that liver failure may lead to œstrogenic changes in the tissues It is presumed that the small concentrations of œstrogens normally released into the circulation from the testis and the adrenal cortex remain active for longer periods than normal because the liver cells are unable to conjugate these

Why do these hormones not remain unconjugated and so continue to act upon the tissues ? One can only conclude that the balance of production and inactivation of *steroid hormones is disturbed in liver failure in such a way as to favour excessive* œstrogen activity

ULCERATIVE COLITIS

One example of gynæcomastia associated with ulcerative colitis has appeared in the literature [22] The history and findings were typical of severe ulcerative colitis, which resisted conservative treatment and eventually required ileostomy and finally colectomy The gynæcomastia was unilateral at first and made its appearance during a relapse Subsequently, both breasts were affected and the patient's *condition deteriorated to such an extent that colectomy was performed* Liver biopsy at this time showed " parenchymal degeneration and fibrosis " After the operation of colectomy the patient's general health improved, and the gynæcomastia disappeared It is known that ulcerative colitis can lead to the development of cirrhosis of the liver,[23, 24, 25] and in the absence of further examples of gynæcomastia in association with ulcerative colitis it may be suggested, as a hypothesis, that gynæcomastia under these circumstances is the result of liver cell damage

HÆMOCHROMATOSIS

If liver cell damage is the cause of gynæcomastia in cirrhosis of the liver, it would be expected that any disease which caused sufficient liver cell failure would cause gynæcomastia This is true of acute infective hepatitis, cardiac cirrhosis and carcinoma However, hæmochromatosis does not appear to cause gynæcomastia Neither Sheldon[34, 35] nor Lawrence,[36] *both of whom have studied this disease* extensively, has encountered gynæcomastia as a complication of hæmochromatosis

In order to explore this paradox further, two patients suffering from hæmochromatosis were studied at Guy's Hospital, and autopsy material from a third was obtained.

CASE I The patient, who was aged 34 years, complained of fatigue, loss of libido, impotence and darkening of the skin for three years On examination the skin showed a dark greyish discoloration, especially on the face and hands The liver was enlarged to the umbilicus , pubic,

was palpable three inches below the left costal margin Pubic and axillary hair was scanty. The testes were normal in size but soft, and the urine showed intermittent glycosuria

The patient died (aged 48 years) as the result of hæmatemesis At autopsy findings typical of hæmochromatosis were discovered The testes showed arrest of the germinal epithelium at the stage of secondary spermatocytes, normal interstitial cells, and scanty deposits of iron in the walls of some blood vessels The anterior pituitary gland showed extensive deposits of iron, especially in the basophil cells (Figure 17)

TABLE XXIII

Day	Urinary 17-Ketosteroids (Mg /24 hours)	Chamber Eosinophil Count (Cells/cm)
First	9 1	
Second	8 8	
Third	8 7	130
Fourth	11 8	120
Fifth ACTH, 25 units (intramuscular injection)	7 4	110 ↓ 50 (4 hours after intramuscular injection of ACTH)
Sixth	10 8	75

From the data shown in Table XXI the following conclusions may be drawn.

(1) All three patients suffered from typical hæmochromatosis

(2) Low urinary gonadotrophin levels suggest that the symptoms of gonadal failure may result from failure of adenohypophysial secretion of gonadotrophins

(3) Normal Kepler and normal 17-ketosteroid excretion, together with normal serum electrolyte levels and a prompt fall in circulating eosinophils after injection of ACTH, indicates normal adrenocortical function Failure of circulating eosinophils to fall after the administration of adrenaline suggests that the capacity of the pituitary to produce or to release ACTH may be defective, although doubt has been cast upon the significance of this test

(4) Testicular biopsy stained by Perls' reagent showed very little iron, and that in such places as to make it improbable that the deposition of the metal was responsible for the testicular failure The appearance of the germinal epithelium is compatible with failure of gonadotrophic function of the pituitary

(5) The autopsy appearance of the adenohypophysis provides a possible explanation for the failure of gonadotrophin secretion

Although hæmochromatosis frequently causes testicular atrophy, impotence and loss of body hair, these changes are not associated with gynæcomastia, in contrast to other forms of liver disease which not infrequently cause gynæcomastia in addition to these other changes The findings presented above indicate that extensive deposits of iron are found in the basophil cells of the anterior pituitary gland, but that the testis escapes all but the slightest invasion by the metal Similar findings were reported by Hubble [83] This would suggest that testicular failure results from defective pituitary function rather than from failure of the testis *per se* The pituitary origin of this hypogonadism is further indicated by testicular biopsy, which reveals normal Leydig cells but arrest of spermatogenesis at the stage of secondary spermatocytes, and by low values or absence of urinary gonadotrophins and by response to chorionic

axillary and body hairs were scanty, while the beard required shaving only twice weekly, whereas the patient had formerly shaved every day. The skin of the face was soft, and the testes were smaller than normal and soft. The following investigations were performed in addition to those shown in Table XXI.

(1) Thorn test (Table XXII). The response to this indicates normal adrenocortical function. The failure of response to adrenaline was at that time (1952) taken as evidence in favour of pituitary failure, but this conclusion would now be considered unjustified.

(2) Testicular biopsy. In the tubules the basement membrane was normal. In the germinal epithelium arrest of spermatogenesis was apparent at the stage of secondary spermatocytes. In the interstitial tissue Leydig cells were normal in number (seven per tubule) and appearance. Perls' stain showed the deposition of iron in small amounts in the walls of some of the smaller blood vessels, but none in the germinal epithelium.

(3) Testosterone caused a return of sexual activity, stimulated the growth of facial hair, and produced a sense of well-being.

TABLE XXII

Day	Urinary 17-Ketosteroids (Mg./24 hours)	Chamber Eosinophil Count (Cells/c mm.)
First	4 9	80
Second .	4 1	70
Third ACTH, 30 mg (intravenous injection) during 12-hour period	8 5	100 ↓ 0 (at the conclusion of intravenous injection of ACTH)
Fourth	9 1	37
Fifth	6 2	78
Sixth Adrenaline (1 1000) 0 3 cm (hypodermic injection)	—	50 ↓ 53 (4 hours after hypodermic injection of adrenaline)

CASE II.—At the age of 47 years the patient's friends drew his attention to the dark colour of his skin, which became more pronounced during the eight years before the present studies were undertaken. Six years after the onset of the change in skin colour the patient became impotent, and two years later diabetes was discovered. The latter responded to insulin treatment but remained difficult to stabilize. On examination the skin was grey in colour, and the liver was palpable four inches below the costal margin. Axillary and pubic hair were almost absent, body hair was scanty, and the testes were smaller than normal. The following investigations were performed in addition to those shown in Table XXI.

(1) Thorn test (Table XXIII). This test indicates normal adrenocortical function.

(2) Testicular biopsy. In the tubules the basement membrane was normal. In the germinal

(3) Response to chorionic gonadotrophin. After a course of intramuscular injections of chorionic gonadotrophin (1000 units twice weekly for three weeks), the patient experienced a return of libido and erections. The testes increased in size and became tender. No change in the distribution of hair throughout the body was noticed.

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gonadotrophin (Case II). Response to intramuscular injection of testosterone (Case I) indicates that the tissues were not unresponsive to testicular androgens Failure of the anterior pituitary to secrete gonadotrophins suggests two possible explanations for the absence of gynæcomastia In the first place absence of normal stimulation of the testis may interfere with the secretion of œstrogens; hence, even when liver failure becomes advanced, the blood contains no œstrogens to be inactivated, and hence breast stimulation does not occur In the second place œstrogens do not cause stimulation of the breasts in hypophysectomized animals (page 24) Which of the hormones of the adenohypophysis are required to permit

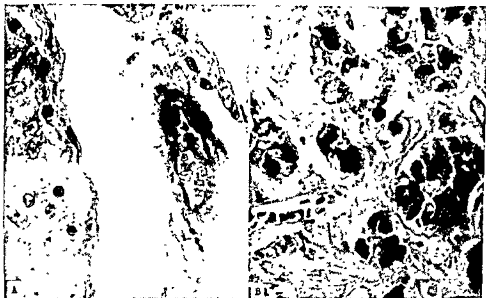


FIGURE 17
Hæmochromatosis (A) Testes (Perls' stain) Small deposits of iron can be seen in the walls of a blood vessel The germinal epithelium and Leydig cells are free of iron (B) Anterior pituitary gland (Perls' stain) Extensive deposits of iron can be seen in the basophil cells

œstrogenic breast stimulation remains unknown However, absence of gonadotrophins may interfere with the capacity of unconjugated œstrogens to cause gynæcomastia The urinary œstrogen levels found in Cases I and II suggest that these hormones are not entirely absent, although testicular failure was present Our present knowledge of normal male œstrogen excretion does not enable one to comment on these results

There is reason to suppose that the secretion of gonadotrophins is the most vulnerable function of the adenohypophysis, being the first to suffer in diseases of this structure [43] Pituitary failure has been recorded in other cases of hæmochromatosis,[44, 45] and it seems more likely that this is responsible for the absence of breast stimulation than failure of œstrogen secretion

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CHAPTER XI

GYNÆCOMASTIA ASSOCIATED WITH MALNUTRITION

During the second world war a considerable number of American soldiers developed *gynæcomastia during their stay in* Japanese prison camps, where they were [illegible] For example Musselman[1] described the appearance

were noticed

Jacobs[2] studied the largest group of cases His experience concerned 9000 prisoners, of whom 2400 died within the first 18 months, death being due directly or indirectly to malnutrition After they had been two years in the camp a series of Red Cross parcels began to arrive, and for four months the diet of all the men was adequate Thereafter they returned to a state of malnutrition, and this state of affairs persisted until the time of release 22 months after the arrival of the first parcels (four years after imprisonment).

At the time of arrival of the first Red Cross parcels there were no known cases

hospital

Subsequently Jacobs estimated that 50% of the prisoners noticed some gynæcomastia after release and that all those who had shown gynæcomastia in the camp reported a return of this symptom Return of libido and testicular pain were noticed at the time the gynæcomastia appeared

Jacobs saw gynæcomastia only during refeeding

Because of the vast number of vitamin deficiency diseases it was natural to attempt to explain

minimal and barely compatible with life

Hibbs[3] studied 34 cases of gynæcomastia among 8000 prisoners The gynæcomastia occurred after 18 months in the prison, which represented an interval of 12 months between the last appearance of a new manifestation of dietary deficiency and *the first case of gynæcomastia The gynæcomastia was noticed during improvement* in the diet from 1200 to 1400 Calories The men affected had all been malnourished and underfed, but were not necessarily the most severely affected Usually the condition appeared when the prisoners gained weight, and for the most part the men were affected at the same time—almost like an epidemic Platt[20] made similar observations

Klatskin and his colleagues[4] studied a group of 300 men who, after their release from prison camps, were admitted to hospital for the treatment of malnutrition. They had been in Japanese hands between April, 1942, and September, 1945. In August, 1945, food parcels began to arrive The authors began their studies in December, 1945 Among 300 men, 48 showed gynæcomastia, of which 17 cases occurred following return to a normal diet, and another seven were aggravated

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with impotence, loss of libido, testicular atrophy and loss of body hair, the other appearing during refeeding with the return of sexual activity.

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lysis.

Various studies have also been made of hormone metabolism in malnutrition Jailer[8] implanted pellets of œstradiol into the spleen of spayed female rats and fed them a diet deficient in vitamin B complex until they lost 28% of their weight. Continuous œstrus effects were seen in vaginal smears, and this finding was not altered by addition of thiamine and riboflavine to the diet. Jailer concluded that inanition and not lack of vitamin B was responsible for failure of the liver to inactivate œstradiol

On the other hand, Segaloff and Segaloff[9] showed that vitamin B deficiency leads to a decline in the capacity of rat liver to inactivate œstrone and œstradiol and also to a diminished response of rat tissues to subcutaneous injection of œstradiol. These effects were prevented by the administration of thiamine and riboflavine. Drill and Pfeiffer,[10] however, showed that inanition in the presence of adequate vitamin B would cause a decline in the ability of the rat's liver to inactivate œstrone and œstradiol

Unna and his colleagues[11] believed that methionine was the important factor required to maintain the capacity of the liver to inactivate œstrogens They showed that rats kept alive on low protein diets cannot retain normal amounts of riboflavine in their livers Methionine counteracts this fall in the riboflavine content of the liver The liver of such rats kept on a low protein diet for three months failed to inactivate œstradiol, but methionine restored this capacity even when low protein intake continued

These studies suggest two possible explanations for the gynæcomastia of malnutrition. Firstly, it is possible that return to normal diet brings about a return of testicular activity before the liver regains the capacity to inactivate œstrogens Secondly, the reawakening of testicular activity after a period of malnutrition may bring about changes like those seen at puberty. Implicit in both hypotheses is the idea that testicular function remains in abeyance during malnutrition, an idea which is supported by the absence of libido and of erections and by the experiments with malnourished mice mentioned above This temporary

normal gland in hypophysectomized mice

The first theory has not been supported by any direct evidence However, it will be recalled that in Malaya a diet of polished rice produced beriberi, but if beriberi was treated with pure thiamine, without change in the diet, pellagra appeared Pellagra never appeared before beriberi [14] This phenomenon has been reported by a number of workers [15, 16, 17, 18] It would seem that an emergency pathway is established during deficiency of one substance which temporarily renders another unnecessary In the case of gynæcomastia it may be supposed that during malnutrition the liver can inactivate œstrogens by means of metabolic pathways which do not require some component of the vitamin B complex, but that when normal feeding is resumed, the need for vitamin B returns, and this is expressed by the appearance of gynæcomastia This concept is without any experimental support, and in view of the fact that malnutrition interferes with the capacity of the liver of

by improvement of the diet; 31 occurred during starvation. The breasts were tender in every case, and both sides were more often affected than one, although sometimes asynchronously. One breast subjected to histological examination revealed the changes typical of gynæcomastia (see page 22). It was estimated that the average diet of these men consisted of approximately 1735 Calories (protein 42 grammes, fat 7 grammes and carbohydrate 375 grammes). On this diet they

All the

tis, while one-third showed hepatomegaly or abnormal response to liver function tests, or both. One-third had small testes as measured by a flexible metal ruler. Body hair was normal in every case. The 17-ketosteroid excretion and urinary œstrogen values were low, but urinary gonadotrophin values were normal.

Zurbiran and Gómez-Mont[5] had the advantage of applying modern laboratory methods to the study of malnutrition. They described the testis in malnutrition as showing decrease in the size of tubules, thickening of the basement membrane and defective spermatogenesis. The germinal epithelium was almost always involved, sometimes showing arrest of maturation, at other times showing an over-all lack of germinal cells. Interstitial cells were few in number, small in size, and loaded with brownish pigment. These changes in the Leydig cells were said to resemble those seen in animals during periods of sexual inactivity. Similar changes in testicular histology are seen in malnourished animals,[13] and Zurbiran and Gómez-Mont believe that the human testis in malnutrition resembles that found in pituitary tumours with low urinary gonadotrophins.[13]

Zurbiran and Gómez-Mont also found low urinary 17-ketosteroid levels in both sexes. The mean figure for men was 3·5 mg. and for women 2·4 mg. per 24 hours. This suggests that both the testicular and adrenal contributions may be diminished, since the total level was low in b

in every male patient in whom th

low in 79% and raised in 21%

trophin and urinary œstrogen le

this increase in œstrogen excretion was very great and was almost always followed in men by gynæcomastia, which outlasted the duration of the raised urinary œstrogen excretion. Unfortunately the authors do not indicate the exact correlation between high urinary œstrogens and gynæcomastia.

During the period of malnutrition about 20% of malnourished men showed gynæcomastia and 21% showed raised urinary œstrogen levels. On the other hand, a return to normal diet was associated with gynæcomastia in almost every case, and a rise in urinary œstrogens to levels above normal was also almost universal. The authors studied 201 patients suffering from malnutrition and concluded that the fundamental endocrine abnormality was deficient pituitary function.

Landau and his colleagues[12] studied the effect of starvation upon the urinary output of 17-ketosteroids and androgens in three normal men and one obese woman. During a four-day period of fasting the 17-ketosteroid output fell by 50%, and the androgen content of the urine showed a parallel drop.

Kark *et alii*[6] studied the effect of malnutrition by refeeding men with cirrhosis of the liver who were poorly nourished. They selected men suffering from established

The patients complained of loss of libido,

testes and needed to shave only two or three

was enlarged. The patients were given diets

uring this period of refeeding hair returned on

icker. Return of libido and erections was

he testes.

Kark *et alii* expressed the belief that there were two types of gynæcomastia associated with cirrhosis of the liver, one during the height of the disease, associated

with impotence, loss of libido, testicular atrophy and loss of body hair, the other appearing during refeeding with the return of sexual activity.

These clinical studies have been amplified and supported by animal experiments. Mason and Wolfe,[7] for example, found that they could restore hypophysectomized

[illegible] If the donor were [illegible] ough viable. This [illegible] ophysis

Various studies have also been made of hormone metabolism in malnutrition. Jailer[8] implanted pellets of œstradiol into the spleen of spayed female rats and fed them a diet deficient in vitamin B complex until they lost 28% of their weight. Continuous œstrus effects were seen in vaginal smears, and this finding was not altered by addition of thiamine and riboflavine to the diet. Jailer concluded that inanition and not lack of vitamin B was responsible for failure of the liver to inactivate œstradiol.

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These studies suggest two possible explanations for the gynæcomastia of malnutrition. Firstly, it is possible that return to normal diet brings about a return of testicular activity before the liver regains the capacity to inactivate œstrogens. Secondly, the reawakening of testicular activity after a period of malnutrition may bring about changes like those seen at puberty. Implicit in both hypotheses is the idea that testicular function remains in abeyance during malnutrition, an idea which is supported by the absence of libido and of erections and by the experiments with malnourished mice mentioned above. This temporary [illegible]

the pituitary gland of mice subjected to starvation could not substitute for the normal gland in hypophysectomized mice.

[illegible]

Pellagra never appeared before [illegible] [14] [illegible]
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unnecessary. In the case of gynæcomastia it may be supposed that during malnutrition the liver can inactivate œstrogens by means of metabolic pathways which do not require some component of the vitamin B complex, but that when normal feeding is resumed, the need for vitamin B returns, and this is expressed by the appearance of gynæcomastia. This concept is without any experimental support, and in view of the fact that malnutrition interferes with the capacity of the liver of

rats to inactivate œstrogens during the period of deficiency it does not seem very probable. Moreover, the observations of Zurbiran and Gómez-Mont make it likely that the secretion of œstrogens is diminished during malnutrition. It seems more probable that the gynæcomastia of refeeding is associated with the reawakening of sexual activity which occurs at that time. The return of testicular function probably resembles the endocrine activity seen at puberty, and it is possible that the same mechanism which produces the subareolar node at that time may play a part in the occurrence of gynæcomastia during refeeding. During malnutrition the testis is smaller than normal, and spermatogenesis is depressed[5] On refeeding, tenderness and swelling of the testes are noticed, and the whole process resembles a second puberty. The ætiology of this type of gynæcomastia is therefore expected to be the same as The same would apply to gynæcomastia seen in

On the other hand, gynæcomastia sometimes appears during the period of malnutrition. This may be explained by the fact that some 20% of men show an increased urinary excretion of œstrogens during starvation. Why some men show a annot be explained. There is no the malnutrition is important tion with a number of diseases which cause wasting, e g pulmonary tuberculosis. Wheeler *et* ciated with these conditions is due t owever, the cases so far reported have indicated that no close correlation exists between wasting and gynæcomastia In these cases gynæcomastia has appeared at the height of the illness and has usually undergone remission with the associated disease

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CHAPTER XII

DRUGS AS A CAUSE OF GYNÆCOMASTIA

A number of drugs, including certain hormones, can cause gynæcomastia In some cases (e g. œstrogens) breast stimulation is to be expected and occurs in a predictable fashion However, in the case of other drugs gynæcomastia is sporadic and totally unexpected (e g digitalis) The following drugs can cause gynæcomastia

(1) Œstrogens
(2) Androgens.
(3) Chorionic gonadotrophin.
(4) Adrenocortical hormones.
(5) Digitalis.
(6) Amphetamine
(7) Radioactive iodine.
(8) Reserpine

ŒSTROGENS

When adult males take œstrogenic substances, a number of changes result, including loss of libido, impotence, gynæcomastia, diminution in testicular size and destruction of the germinal epithelium Some of these changes (loss of libido,

actic

the

char ... germinal epithelium (ii) Thickening of the walls of the tubules. (iii) Absence of Leydig cells (iv) Interstitial fibrosis These changes were described in men past their middle years, and some of the effects mentioned could be attributed to age Dunn[2, 3, 38] studied testicular biopsies taken from a 27-year-old man who received 530 mg of stilbœstrol by mouth during a period of

function (libido, erections and emissions) did not return to normal for a further month

In the case of a boy ag...
testicular biopsy showed (i)
(ii) sclerosis of the walls of

Greep and Jones[5] described experiments which raise the possibility that these changes are due not to a direct effect upon the testis, but to suppression of the secretion of gonadotrophins by the adenohypophysis They compared the gonadotrophic

Lynch ... studied the testes ...
(control
pregnar
showed ... weights of 3 0 gm, the second of 1 6 gm, and the third of 3·0 gm This suggests that follicle-stimulating hormone administered together with œstrogen prevents the testicular atrophy which œstrogens alone produce, and hence



FIGURE 18

(A) and (B) The testis before

rapy
bules
e of

contain only Sertoli cells
degeneration

that œstrogens produce testicular atrophy by suppressing the secretion of follicle-stimulating hormone. The testes of the œstrogen-treated group returned to normal when treatment was stopped, and testicular weight also returned to normal.

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treat

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hypertrophy by supposing that œstrogens suppress the secretion of follicle-stimulating hormone and stimulate the release of interstitial-cell stimulating hormone. They produced "tumours" of Leydig cells by injections of interstitial cell-stimulating hormone

's Hospital, where

other respect, were

were taken before

and after treatment; urinary 17-ketosteroids, œstrogens and gonadotrophins were also measured before and after the administration of stilbœstrol Table XXIV shows the results of these assays in the first patient. It can be seen that the 17-ketosteroid levels show no consistent change and that the changes in œstrogen excretion are not striking The first implantation of stilbœstrol did not alter the level of urinary gonadotrophins, although it caused serious changes in endocrine function

After the second implantation urinary

the stilbœstrol had caused considerable

patient the β-fraction of urinary 17-keto-

ntation.

Testicular biopsy before treatment was normal, but after two implantations of

cells were very pale and showed an increase in granules, and the cytoplasm had a "ragged" appearance The Leydig cell count before treatment was 17·5 per tubule and after treatment 7·0 per tubule

Testicular biopsy eight weeks after the second biopsy (Figure 18) showed the following changes: Some thickening of the basement membrane was seen In the germinal epithelium, normal spermatogenesis was absent, and most tubules were lined by Sertoli cells only In the interstitial tissue, Leydig cells showed further reduction in number The cytoplasm of these cells was very pale and granular. The cells were too few in number to count in relation to the tubules.

Part of this spec

method of Schultz

at the side of the ce

described in animals treated with œstrogens.[4]

The studies performed on the second patient are shown in Table XXV. Again the 17-ketosteroid levels show no consistent change Although a fall is seen, all readings are within normal limits, and the β-fraction showed no change following implantation Urinary gonadotrophins and urinary œstrogens also showed no consistent changes Implantation of stilbœstrol caused impotence, gynæcomastia and pigmentation of the nipples. Testicular biopsy after treatment showed the defective spermatogenesis with undifferentiated germinal cells, Leydig cells were normal in distribution but pale-staining and granular with ragged cytoplasm

A third patient showed considerable hyalinization of the basement membranes and similar appearances in the Leydig cells From this specimen one part was fixed in digitonin and stained by the method of Schultz This showed blue staining



FIGURE 18

[illegible] (A) and (B) The testis before

contain only Sertoli cells Leydig cells [illegible]
degeneration

The third patient, at the age of 17 years, received 1 mg of stilbœstrol daily for 28 days This treatment produced gynæcomastia and impotence for a period of one month. Thereafter, normal sexual function returned Three years later testicular biopsy gave normal findings and the Leydig cell count revealed 14 cells per tubule (Figure 19)

Such doses of œstrogen therefore produce only reversible changes. The persistent impotence in the first patient was incomplete and possibly perpetuated by psychological factors. A slight degree of gynæcomastia remained, which emphasizes the previous observation that gynæcomastia can persist to some extent long after the removal of the exciting cause (see page 31)

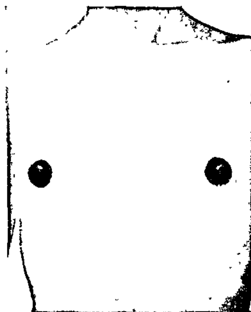


FIGURE 20
The gynæcomastia and characteristic pigmentation of the nipples following large doses of stilbœstrol

Minute doses of œstrogen can cause gynæcomastia This was seen in men handling œstrogens during the manufacture of tablets [9] In drug factories it has been shown that absorption through the skin or by inhalation can cause gynæcomastia, and that at low concentrations some men are more resistant than others Gynæcomastia can precede or occur without pigmentation of the nipples and without impotence This suggests that gynæcomastia results from direct action upon the breasts in concentrations too small to affect the testes

Children appear to be highly susceptible to small doses of œstrogenic substances For example, a worker handling œstrogens in a factory where other men had been affected by gynæcomastia was not himself affected by gynæcomastia His son,
a
f
r
s
œstrogen in his hair (which was not washed at work).[11] Indicative also of the sensitivity of the young breast to minute amounts of œstrogen is the observation that

in Leydig cells and in that part of the Sertoli cells nearest the basement membrane, indicating the deposition of cholesterol and cholesterol esters at these sit

In contrast to these acute experi–
the testis was studied in
of acne.

The first patient received an implant of 200 mg. of stilbœstrol at the age of 16 years At 25 years the patient showed slight gynæcomastia and complained of impotence. Investigations revealed the following findings:

Urinary 17-ketosteroids (mg per 24 hours) · 17·6; 10·0, 9·0

Urinary gonadotrophins (mouse units per 24 hours): $>12<16$; $>12<16$; $>12<16$.

Semen. Two counts showed 53×10^6 and 109×10^6 per cubic centimetre respectively and in each case motility was 2.

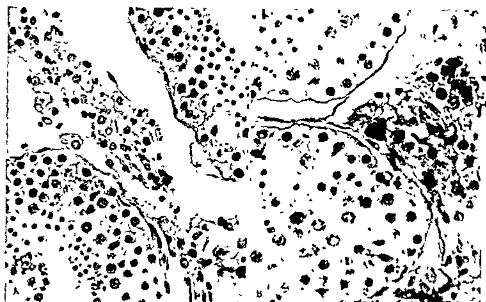


FIGURE 19

The testis following œstrogen therapy (A) High-power view showing normal tubules and interstitial tissue The patient had received stilbœstrol nine years before this biopsy was taken (B) High-power view showing normal tubules and interstitial tissue in a patient who had received stilbœstrol three years before this biopsy was taken

Testicular biopsy gave normal findings, and the Leydig cell count was 13 1 cells per tubule (Figure 19)

The second patient had received an implant of 300 mg of stilbœstrol at the age of 16 years Gynæcomastia and impotence followed, but the symptoms gradually disappeared after about six months At the age of 27 years sexual function was normal, and no evidence of gynæcomastia was found Investigations revealed the following findings

Urinary 17-ketosteroids 14 4 mg /24 hours

Urinary gonadotrophins $>16<24$ mouse units/24 hours.

Semen Two counts showed 80×10^6 and 112×10^6 per cubic centimetre respectively, and in each case motility was 3

Testicular biopsy gave normal findings The Leydig cell count showed 14 cells per tubule.

TABLE XXV

Time after Treatment	17-Keto-steroids (Mg./24 Hours)	Urinary Gonadotrophins (Mouse Units/24 Hours)	Urinary Œstrogens (µg./24 Hours)			Testicular Biopsy				Semen			Potency	Gynæcomastia
			Œstrone	Œstradiol	Œstriol	Tubules: Basement Membrane	Tubules: Epithelium	Leydig Cells: Number	Leydig Cells: Appearance	Volume	Motility	Number		
Before treatment	11·0 15·0	12–16 12–36	0·5	0·5	13	Normal	Normal spermatogenesis	21/tubule	Normal	3·5	2·5	84 × 10⁶	Normal	Absent
Implantation 300 mg. stilbœstrol														
7th day	13·6	12–16								3·2	0·5	0·3 × 10⁶	Absent	Grade III
8th day			0·5	0·5	0·5								Absent	Grade III
9th day	7·5	12–16											Absent	Grade III
32nd day						Normal	Sertoli cells only	4/tubule	Pale granular cytoplasm				Absent	Grade III
56th day	8·4	12–16									–	–	Absent	Grade III

TABLE XXIV

Time after Treatment	17-Ketosteroids (Mg./24 Hours)	Urinary Gonadotrophins (Mouse Units/24 Hours)	Urinary Œstrogens (µg./24 hours)			Testicular Biopsy				Potency	Gynæcomastia
						Tubules		Leydig Cells			
			Œstrone	Œstradiol	Œstriol	Basement Membrane	Epithelium	Number	Appearance		
—	—	—	—	—	—	—	—	—	—	—	—
Before treatment	13.6 12.0 13.0	>12 <16 12 <16 12 16	3.4	1.7	17	Normal	Normal spermatogenesis	17.5/tubule	Normal	Normal	Absent
Implantation 300 mg. stilbœstrol											
3rd day	—			—	—	—	—	—	—	Declined	Grade II
11th day	10.0	>12 <16		—	—	—	—	—	-	Absent	Grade III
38th day	11.0	12 <16		—		—	—	—		Absent	Grade III
40th day			0.9	0.4	35	—	—	—	—	Absent	Grade III
44th day	10.8	—		—		—	—	—	—	Absent	Grade III
80th day	13.6	12 16	—	—		—	—	—	—	Absent	Grade III
84th day			2.5	3.1	29		—	—	—	Absent	Grade III
Implantation 300 mg. stilbœstrol											
97th day	19.0	>32 <64		—	—	—	—	—	—	Absent	Grade III
121st day	—		—	—	—	Normal	Arrest at spermatid stage	7.0/tubule	Pale granular cytoplasm	Absent	Grade III
127th day	12.4	>48 <64		—	—	—	—	—	—	Absent	Grade III
177th day	—		—	—	—	Some thickening	Sertoli cells only	Grossly reduced	Ragged cytoplasm	Absent	Grade III

remains within normal limits.
action of œstrogens upon the
œstrogens affect the testis b
cannot be excluded, because
are semiquantitative at best,
that the 17-ketosteroids output (including the β-fraction) remains normal is evidence against gross disturbance in adrenocortical function following œstrogen therapy Presumably, gynæcomastia following the administration of œstrogens is due to direct action upon the breast.

ANDROGENS

Several reports of gynæcomastia in men receiving methyl testosterone have appeared in the literature.[10, 11] At Guy's Hospital 101 patients who had received androgen therapy were examined and questioned concerning changes in the breasts during or after treatment The patients fell into five groups.

(1) Seven patients who received testosterone under the age of 20 years for delay in the obset of puberty

(2) Thirteen patients who received testosterone after the age of 20 years for some defect in the development of secondary sexual characteristics, e g , unbroken voice, small genitals, poorly developed beard, delay in the onset of puberty

(3) Nine adult castrates receiving testosterone as substitution therapy.

(4) Twenty-five adults receiving androgens for eunuchoidism and infantile genitalia

(5) Forty-seven patients suffering from psychogenic impotence with no evidence of abnormal endocrine function

Among these patients, three had suffered from gynæcomastia while receiving androgens The preparations used included tablets of methyl testosterone, intramuscular injections of testosterone propionate and implants of testosterone

enlar
four
tube
table
The implant provided effective substitution therapy but did not cause gynæcomastia.

The second patient was aged 32 years and had suffered psychogenic impotence for five years Physical examination, testicular biopsy and estimations of urinary 17-ketosteroid excretion and urinary gonadotrophin level all gave normal findings. The patient was given weekly injections of testosterone propionate (25 mg) for 32 weeks At the end of this time he complained of painful breasts, and examination revealed a tender " button " of breast tissue behind the areolæ The injections were replaced by tablets of methyl testosterone (25 mg daily), and within three days the breasts returned to normal

The third patient, aged 29 years, was also an example of psychogenic impotence of six years' duration He had been given intramuscular injections of testosterone propionate weekly for 24 weeks and was then given methyl testosterone tablets
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of a
after injections of testosterone propionate Gynæcomastia is not usually an immediate effect of androgens, but generally follows some months of intensive therapy.

ıalation of œstrogens from the urine of
when the horses were kept in stables by

Sometimes the source of œstrogen is not obvious, and careful enquiry is needed *in cases of unexplained gynæcomastia. Children, for example, may take tablets in* mistake for sweets. A boy of four years was seen with gynæcomastia which resulted ... omastia ... trol, for ... within *two weeks of stopping this treatment*

TABLE XXVI
Gynæcomastia following Œstrogen Therapy

Case Number	Age at Time of Treatment (Years)	Œstrogen and Total Dose (Mg.)	Number of Implants	Extent of Gynæcomastia during Treatment (Grade)	Duration of Transitory Gynæcomastia	Duration and Severity of Permanent Gynæcomastia
Case LIX	16	Stilbœstrol 200	1	II	—	>9 years <grade I
A B	17	Stilbœstrol 200	1	I	6 months	—
M B	16	Stilbœstrol 200	1	I	4 months	—
Case LX	16	Stilbœstrol 200	1	I	2 years	—
E C	17	Stilbœstrol 200	1	I	3 months	—
J C	16	Stilbœstrol 200	1	I	2 months	—
J D	16	Stilbœstrol 700	4	II	9 months	—
Case LXI	21	Stilbœstrol 600	3	II	10 months	—
C E	17	Stilbœstrol 200	1	II	8 months	—
Case LXII	15	Œstradiol 400	2	I	—	>12 years <grade I
Case LXIII	18	Stilbœstrol 500	2	I	8 months	—
D I	16	Stilbœstrol 700	4	I	3 months	—
J L	16	Stilbœstrol 400	2	I	4 months	—
W L	15	Stilbœstrol 300	2	II	6 months	—
Case LXIV	21	Stilbœstrol 300	2	II	—	>6 years <grade I
G R	17	Stilbœstrol 400	2	II	6 months	—
S V	18	Stilbœstrol 600	2	I	6 months	—

... the ... d in ... nta-tion of ... streak of pigmentation on the abdominal wall bel ... that seen during pregnancy Although these si... the possibility ... to œstrogens ... intense pigmentation of the nipples, which become ... pigmentation is permanent, although it may fade to ... stopped

The action of œstrogens upon the testis therefore involves quantitative and qualitative changes in the Leydig cells, together with arrest of spermatogenesis at ... of spermatids and deposition of cholesterol in Leydig and Sertoli cells. ... excretion

remains within normal limits. These findings are compatible with the view that the action of œstrogens upon the testis is a direct one The possibility that exogenous œstrogens affect the testis by depressing [illegible] cannot be excluded, because present meth

action upon the breast.

ANDROGENS

Several reports of gynæcomastia in men receiving methyl testosterone have appeared in the literature.[10, 11] At Guy's Hospital 101 patients who had received androgen therapy were examined and questioned concerning changes in the breasts during or after treatment. The patients fell into five groups.

(1) Seven patients who received testosterone under the age of 20 years for delay in the onset of puberty.

(2) Thirteen patients who received testosterone after the age of 20 years for some defect in the development of secondary sexual characteristics, e g, unbroken voice, small genitals, poorly developed beard, delay in the onset of puberty

(3) Nine adult castrates receiving testosterone as substitution therapy.

(4) Twenty-five adults receiving androgens for eunuchoidism and infantile genitalia

(5) Forty-seven patients suffering from psychogenic impotence with no evidence of abnormal endocrine function.

Among these patients, three had suffered from gynæcomastia while receiving androgens The preparations used included tablets of methyl testosterone, intramuscular injections of testosterone propionate and implants of testosterone

Of the three patients showing gynæcomastia, one, aged 49 years, showed breast enlargement (grade I) after taking tablets of methyl testosterone over a period of four years (25 mg. daily) as substitution therapy following surgical castration for tuberculous orchitis The gynæcomastia subsided within three days of stopping the tablets, and testosterone was given by implantation (600 mg. every six months). The implant provided effective substitution therapy but did not cause gynæcomastia.

The second patient was aged 32
for five years Physical examination
17-ketosteroid excretion and urinary
The patient was given weekly injections of testosterone propionate (25 mg) for 32 weeks At the end of this time he complained of painful breasts, and examination revealed a tender " button " of breast tissue behind the areolæ The injections were replaced by tablets of methyl testosterone (25 mg daily), and within three days the breasts returned to normal

The third patient [illegible]
of six y
propion
(25 mg
tion of

From these studies it will be seen that gynæcomastia is not a common complication of androgen therapy It can occur with methyl testosterone taken by mouth or after injections of testosterone propionate Gynæcomastia is not usually an immediate effect of androgens, but generally follows some months of intensive therapy.

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developed,
' play some
considering
the rarity with which androgens produce gynæcomastia, the delay in its appearance and the large doses required, this view seems unlikely. Furthermore, the action of androgens upon the breast of the monkey produces changes which are unlike the picture of duct hyperplasia seen in cases of gynæcomastia (see page 24) Recent studies have shown that the body is capable of converting certain androgens to œstrogenic substances.[39, 40, 41] This discovery suggests an explanation for the occasional occurrence of gynæcomastia after the prolonged administration of large doses of androgen. Possibly in certain individuals the capacity to convert androgens to œstrogens may be enhanced during prolonged administration of androgens, with the result that sufficient œstrogens are produced to cause stimulation of the breast.

The three patients mentioned above were not submitted to operation on the breasts, but Dr. H F Klinefelter has reported that the breast in gynæcomastia following androgen therapy in one of his patients showed the typical microscopic appearance seen in other forms of gynæcomastia (see page 24)

CHORIONIC GONADOTROPHIN

Chorionic gonadotrophin can produce a " button " of breast tissue behind the areola (see page 33), and in some instances, more severe degrees of gynæcomastia may result Two patients at Guy's Hospital showed gynæcomastia of grade II severity following a course of chorionic gonadotrophin One was submitted to testicular biopsy, which showed (i) Some fibrous thickening of the basement membrane (ii) Normal spermatogenesis and prominent Sertoli cells (iii) Clumps of prominent eosinophilic Leydig cells The appearance of this biopsy suggested *Leydig cell stimulation*

Maddock and Nelson[13] believe this form of gynæcomastia to be the result of Leydig cell stimulation, with consequent secretion of œstrogens (see page 25) Experiments in mice make it seem unlikely that chorionic gonadotrophin acts directly upon the breast (page 70), although possible contamination of this hormone by minute quantities of œstrogen should be considered, also, the action of the hormone upon the breast in man may differ from that seen in animals Until further evidence is at hand, gynæcomastia following injections of chorionic gonadotrophin is best explained as an indirect result of Leydig stimulation which causes the secretion of œstrogens in greater concentrations than normal

ADRENOCORTICAL HORMONES

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Raleigh and Philipson[15] have reported a case of Addison's disease complicated by painful swelling of the right breast This complication appeared after two years' treatment with DOCA and salt. The breast at autopsy showed the usual changes of gynæcomastia.

Lawrence[16] reported the case of a man, aged 32 years, who had been treated for diabetes mellitus by means of insulin for 20 years At this time he developed Addison's disease, which was complicated by a typical crisis after one year. This

given conflicting results,[22, 23, 24] but it seems likely that this hormone acts synergistically with the stimulating effect of œstrogens upon duct growth (see page 26)

So far, no case of gynæcomastia has been reported in untreated subjects of Addison's disease or in patients treated with cortisone Neither have DOCA and eschatin been found to cause gynæcomastia in patients subsequently shown not to be suffering from Addison's disease

The reported cases of gynæcomastia following treatment with eschatin and DOCA occurred under such circumstances as to suggest that these drugs themselves were directly or indirectly responsible for the stimulation of the breasts and not the disease itself It seems likely that either these drugs cause gynæcomastia by direct stimulation of the breast or that some substance formed during their metabolism is responsible for this change Why so few patients have shown such a response cannot be explained

DIGITALIS

Le Winn[25, 26] has reported 14 cases of gynæcomastia appearing during the administration of digitalis Among the first eight, five showed complete remission when the administration of digitalis was discontinued, and recurrence when the drug was resumed In every case the gynæcomastia gradually lessened after several months, even though treatment with digitalis was continued. The ages of the affected patients ranged from 53 to 77 years, and the cause of cardiac failure was

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were examined

in two cases and showed the typical appearance of gynæcomastia

In four of seven patients the bromsulphalein test indicated some degree of impaired liver function, and in six of seven the cholesterol-ester levels were low

normal It will be recalled that Morrione[27] showed that gynæcomastia was seen when

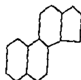
liver disease was severe, and was inconstant in cardiac cirrhosis. In the 14 cases described by Le Winn, cardiac failure was of recent onset and showed a good response to digitalis. The present author has encountered two examples of intense breast stimulation in post-menopausal women soon after the patients were given digoxin (0·75 mg daily). The tenderness and swelling of the breasts subsided when the drug was discontinued, and reappeared when it was resumed Digitoxin did not cause breast stimulation in these patients.

Calov and Whyte[28] reported a case of œdema and painful breasts as toxic effects of digitalis leaf. A woman of 49 years took tincture of digitalis and digitalis leaf for more than two years without ill effect. After a lapse of two years she again took digitalis leaf, but complained of swelling of the feet and hands, which disappeared when the drug was withdrawn. Seven years later she began taking the leaf (0·1 gramme three times a day), and after three days swelling of the legs, groins, buttocks, labia, abdominal wall, arms and breasts occurred " The breasts were swollen, tense, tender with prominent vessels and enlarged, hard, lumpy glandular tissue." The symptoms disappeared two days after the drug was discontinued. The same effects were seen within 24 hours of resuming treatment and were so distressing that the patient stopped the tablets. Digoxin did not produce such symptoms.

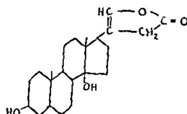
result from the direct action of œstrogens upon the cells themselves (see page 24)

The excretion of digitalis from the body has been studied by Okita and his associates,[29] who used purified isotopically labelled digitoxin administered intravenously They showed that between 60% and 80% of the drug is eliminated either unchanged or as chloroform-soluble metabolites They believe that elimination by the liver and alimentary tract plays only a small part in total excretion. It is possible that the chloroform-soluble metabolites are largely aglycones and their derivatives, which may well have undergone modification in the liver before being excreted in the urine

The chemical similarity between the cardiac glucosides and certain steroid hormones has been considered as important in the effect of these substances upon the breast Both substances contain the cyclopentanoperhydrophenanthrene nucleus:



The distinctive feature of the aglycone molecules of the cardiac glucosides lies in the unsaturated lactone attached to C_{17}, e g



It is tempting to suggest that during the metabolism of this substance changes occur in its structure which produce some steroid hormone capable of stimulating breast tissue

In rabbits, large and continued doses of powdered leaf or digoxin did not produce any histological change in the testis.[14]

One of Le Winn's cases came to autopsy, and the testis (Figure 21) showed the following changes.[30]

Tubules: Basement membranes are normal but spermatogenesis is defective in most tubules and may contain Sertoli cells only.

Interstitial tissue: Leydig cells are very prominent and in places form clumps or large groups.

These changes resemble those seen in other forms of gynæcomastia, but whether this is due to digitalis or to the effects of cardiac failure or to some other cause cannot at present be stated.



FIGURE 21

The testis from a patient who died of congestive cardiac failure. The patient developed gynæcomastia during treatment with digitalis. The basement membranes are normal, spermatogenesis is defective, and Leydig cells appear in large clumps.

The fact that a careful search has failed to reveal similar experiences with digitalis

the preparation of

se of amphetamine

g different prepara-

Le Winn[30] has since discovered other examples of this curious association among patients treated by other physicians. One can only conclude that sporadic examples of gynæcomastia in digitalis therapy have previously passed unnoticed or at least unrecorded, and that minor degrees of breast development could be detected by a more spec

and may

not incon

It is worth noticing that gynæcomastia appears when the patient's general health has improved in a way which recalls gynæcomastia during refeeding after malnutrition. This observation must be taken into account when any explanation of this phenomenon is to be considered.

AMPHETAMINE

Tooley and Lack[31] recorded cases of gynæcomastia occurring in adolescent and adult males receiving amphetamine sulphate for a variety of neurological and psychiatric disorders One girl of nine years developed uterine bleeding during treatment with the same substance. The authors drew attention to a statement by Karnaky,[32] who claimed that amphetamine might cause uterine bleeding in susceptible patients.

July, 1948, and further administration of a new batch of amphetamine to patients

hyperplastic œstrinized endometrium .

These observations suggested the action of some œstrogenic substance which could be traced to a particular batch of amphetamine. It was subsequently shown that these side effects were due to an œstrogenic impurity which was produced during the synthesis of amphetamine During the synthesis of amphetamine, a substance

arouse interest

RADIOACTIVE IODINE

A series of 21 males were given carrier-free radioactive iodine (I^{131}) in doses of between 2 0 and 2 5 mc by Bauer and Goodwin [34] The patients were all suffering from moderately severe thyrotoxicosis, and their ages ranged from 26 to 41 years Six of these patients developed acne and gynæcomastia. The authors suggested that these complications might have resulted from overactivity of the pituitary as the result of the fall in circulating levels of thyroxine which followed I^{131} treatment It was proposed that the adrenal cortex was stimulated as the result of this change in pituitary function However, no other evidence of adrenal stimulation was seen, and *although a fall in circulating thyroxine promotes an increase in the output of* TSH, this causes a fall in ACTH, not a rise [42] The acne could not have resulted from the action of iodide, because a carrier-free preparation was used in which the total amount of iodide would not exceed a fraction of a microgramme

Trunnell and his colleagues[35] studied the distribution of I^{131} at autopsy in the bodies of patients who died after treatment with this substance After the thyroid gland, the pituitary and then the testis were the tissues which absorbed the greatest radioactivity per unit weight The testes showed defective spermatogenesis, which led to the presence of only Sertoli cells within the tubules The breasts showed little evidence of I^{131} uptake

Gorbman[36] showed that similar findings applied to rats given I^{131} in comparable doses The pituitary gland showed changes similar to those seen after thyroidectomy, i e increase in the size of the gland and increase in the number of chromophobe cells These findings were confirmed (also in rats) by Goldberg and Chaikoff [37]

The occurrence of gynæcomastia with acne recalls the presence of these two

I^{131} is associated with sudden stimulation of the testis, with a return to normal

and consequences similar to those encountered at puberty or during the process of refeeding after malnutrition.

On the other hand, the evidence from animal experiments suggests that I^{131}

source of speculation.

RESERPINE

The drugs chlorpromazine and reserpine have recently been reported to cause breast stimulation in male and female patients [45] In one patient gynæcomastia was observed during reserpine therapy, the breasts returned to normal when the drug was stopped. Although these drugs influence the activity of the hypothalamus, no explanation can be offered for the occurrence of gynæcomastia under these circumstances.

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CHAPTER XIII

GYNÆCOMASTIA ASSOCIATED WITH DISEASES OF THE CENTRAL NERVOUS SYSTEM

Certain diseases of the central nervous system may be associated with gynæcomastia, namely

(1) Diseases of the spinal cord (*a*) Traumatic paraplegia, (*b*) Syringomyelia (*c*) Friedreich's ataxia.
(2) Dystrophia myotonica.

Extensive lesions of the spinal cord appear capable of interfering with testicular function, although the mechanism of this interference is uncertain. On the other hand, the disease dystrophia myotonica is associated with a number of changes which are loosely described as "endocrine"; these changes include testicular atrophy, gynæcomastia, baldness and obesity.

DISEASES OF THE SPINAL CORD

Traumatic Paraplegia

In a ward of paraplegic patients Cooper[1] discovered that 22% were suffering from gynæcomastia Of these, two showed raised urinary gonadotrophins, low 17-ketosteroid excretion and azoöspermia. The patients were all young men who had previousl The same worker[8] later studied whom four showed gynæcomastia ients with gynæcomastia showed low urinary œstrogen levels In the more severe cases the patients showed low serum protein values and reversed albumin/globulin ratio, together with a low basal metabolic rate The extent of these metabolic disturbances was roughly proportional to the severity of the spinal injury, but no correlation was found between the occurrence of gynæcomastia and the severity of the metabolic disturbance Cooper and Hoen[2] later reported a further seven examples of gynæcomastia associated with paraplegia

Stemmermann,[3] both by biopsy and at autopsy, studied the testicular histology of patients suffering from paraplegia The germinal epithelium showed defects of varying severity, including Sertoli cells only in some tubules The basement

occurrence of gynæcomastia The number of patients was too small to indicate whether or not such obstruction was a factor, because it was apparent in some cases and not in others Stemmermann referred to the work of Kuntz,[4] who cut the

b

o

of the Leydig cells (see page 62)

Cooper and his colleagues[19] subsequently studied the metabolic changes of paraplegia in greater detail They
a period of catabolism which is cha
nitrogen above the level found in

1

associated with a fall in serum protein level and a decreased albumin/globulin ratio. ndeed, such patients may "starve" to to be proportional to the severity of bolism, 17-ketosteroid excretion falls (in severe cases to less than 2 mg. in 24 hours), and both gonadotrophins and œstrogens are often absent from the urine Liver function tests showed abnormal bromsulphalein retention in three of four patients seen within eight weeks of injury; patients seen later than eight weeks after injury did not show abnormal bromsulphalein retention. This retention of bromsulphalein was not associated with blood loss, fever, transfusion reactions, etc., and was considered by the authors to indicate some impairment of liver function

Of 16 patients with traumatic paraplegia, four showed gynæcomastia and one complained of having suffered this symptom All four showed testicular atrophy, and two others showed testicular atrophy without gynæcomastia Other observers[6, 7] have recorded gynæcomastia in patients with traumatic paraplegia.

These observations suggest that gynæcomastia in traumatic paraplegia could be the result of two changes seen after spinal injury. In the first place, a severe disturbance in nutrition may play some part in the endocrine changes described, although no correlation has been found between and the severity of the nutritional changes The apparently not related to renutrition and a return malnutrition among prisoners of war This point is not in favour of a nutritional cause, because gynæcomastia usually occurs during refeeding rather than during the period of starvation (see page 113) In the second place, traumatic paraplegia can produce changes in the testis which resemble those of Klinefelter's syndrome and other conditions which cause gynæcomastia It seems likely that paraplegia causes

FRIEDREICH'S ATAXIA AND SYRINGOMYELIA

Friec
a rac
of cystic degeneration of the spinal cord

Disturbances of metabolism similar to those described in traumatic paraplegia were seen, and the microscopic appearance of the testis was the same No doubt the same mechanism produces gynæcomastia in all three conditions

DYSTROPHIA MYOTONICA

Since 1947 a number of re

's cells, and the testis showed changes lrome—extensive hyalinization of the

dise
befo

Howard and co-workers[11] describe one patient suffering from dystrophia myotonica and hypogonadism. *He was in an extremely poor* state of nutrition and showed neither clumping of [illegible] nadotrophin levels were low. In [illegible] ated by Dr. H. F. Klinefelter.[12] [illegible] mastia with

TABLE XXVII
Endocrine Studies in Dystrophica Myotonica

Author and Reference	Age (Years).	Examination of Testes	Testicular Biopsy		17-Ketosteroids	Urinary Gonadotrophins	Gynæcomastia
			Tubules	Leydig Cells			
Jacobson *et alii*[14] (8 patients)	28–61	Atrophy in 6	Atrophy frequent	Normal	Low	Normal in the 4 tested	Absent
Sniffen[16] ..	40	Atrophy	Atrophy	Clumping	Normal	High	Present
Nadler *et alii*[16]	56	Atrophy	Hyalinization	Clumping	Low	High	Present
Nadler *et alii*[16]	48	Atrophy	Hyalinization	Normal	Low	Normal	Present
Tierler and Lilienthal[13]	58	?	—	—	Low	Normal	Absent
Martin and Pattee[22]	55	Atrophy	—	—	Low	Normal	Absent
Benda and Bixby[9]	31	Atrophy	Hyalinization	Clumping	Low	High	Absent
Benda and Bixby[9]	*44*	*Atrophy*	*Hyalinization*	*Clumping*	*Normal*	*High*	*Absent*
Caughey and Brown[15]	45	Atrophy	Atrophy	Degeneration	Low	High	Absent
Caughey and Brown[15]	28	Atrophy	Atrophy	Degeneration	Low	High	Absent
De Court *et alii*[14] (5 patients)	—	Atrophy in 5	—	—	Low	—	Absent
Clark *et alii*[17]	26	Atrophy	Atrophy	Clumping	Low Normal	High (I C S H)	Absent
Clark *et alii*[17]	53	Atrophy	Atrophy	Clumping	Low Normal	High (I C S H)	Absent
Klinefelter *et alii*[12]	—	Atrophy	Atrophy	Clumping	Normal	High	Present
Howard et alii[11]	63	Atrophy	Sclerosis	Normal	Low	Low	Absent
Hutchinson and Longson[16]	19	Atrophy	—	—	Normal	Low	Absent
Hutchinson and Longson[16]	21	Atrophy	—	—	Low	Low	Absent
Hutchinson and Longson[16]	35	Atrophy	—	—	Low	Low	Absent
Hutchinson and Longson[16]	45	Atrophy	—	—	Low	High	Absent

persistently raised urinary gonadotrophin levels Testicular biopsy showed the changes described in other cases, and the patient has never shown any clinical evidence of lack of androgens, testosterone in no way affected either the gynæcomastia or the dystrophia myotonica

Other studies of endocrine changes in dystrophia myotonica include those of Jacobson and his colleagues,[14] who claim that 17-ketosteroid excretion is low in males,

Hutchinson and Longson[16] studied four men with dystrophia myotonica. All showed low 17-ketosteroid excretion and low urinary œstrogen levels (estimated by a chemical method). All had small ... three had low FSH values These workers believe ... precede Leydig cell failure. One patient showed n ... low œstrogen levels, and after stimulation with large doses of chorionic gonadotrophin (3000 i u daily by intramuscular injection for seven days) both 17-ketosteroid and œstrogen excretion showed a significant rise The testes in these patients were of normal size but soft consistency.

Clarke and his colleagues[17] studied two patients who suffered from dystrophia myotonica. The average testicular volume was 1·0×1·0×1·3 c cm. The basement membrane did not show hyalinization, but Leydig cells were clumped and possibly increased in number, while urinary androgens and 17-ketosteroids were low. The authors attempted to measure FSH and ICSH separately—the latter by changes in the ventral prostate of the hypophysectomized rat The urinary levels of FSH were normal, but excretion of ICSH was raised

It is perhaps too early to place reliance upon the assay of ICSH excretion, but ... " suggest that high urinary gonado- ... rather than FSH or a mixture of ... port to the idea that the Leydig ...

presented the features of Klinefelter's syndrome, but gynæcomastia was absent. The chief interest in these findings lies in the occurrence of a syndrome like that of Klinefelter, which appears in adult men in association with a disease of the central nervous system It is likely that the mechanism of gynæcomastia in dystrophia myotonica is t ... of high urina ... mechanism ... to the age of ... less frequently with advancing age

Grumbach and his colleagues[25] have reported a case of dystrophica myotonica with Klinefelter's syndrome and female chromosomal sex, while seven cases of the same disease reported by Siebenmann[26] showed hypogonadism and male chromosomal sex

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CHAPTER XIV

GYNÆCOMASTIA ASSOCIATED WITH DISEASES OF THE LUNG

Gynæcomastia has been reported in certain diseases of the lung, namely:

(1) Bronchogenic carcinoma
(2) Pulmonary tuberculosis.[7, 8]
(3) Bronchiectasis.[7]
(4) Empyema [7]

In the case of bronchogenic carcinoma the occurrence of gynæcomastia is such as to indicate an ætiological association between the two conditions. Pulmonary tuberculosis has less claim upon a specific association with gynæcomastia, and it remains to be established that the coexistence of these two conditions is more than coincidental In spite of isolated reports of gynæcomastia in cases of bronchiectasis and empyema, it is likely that these two diseases do not cause breast stimulation, the appearance of which is either fortuitous or at most is precipitated by an acute illness in one already predisposed to gynæcomastia from some other cause.

BRONCHOGENIC CARCINOMA

In 1941 del Castillo[1] and his colleagues reported three cases of bronchogenic carcinoma complicated by gynæcomastia and hypertrophic osteoarthropathy, and in 1944[2] they reported a fourth patient showing the same clinical syndrome

A man of 63 years noticed pain and swelling of his right knee, and later other
occurred, and one year
Loss of libido, impotence
acutely tender and the

lost 30 pounds in weight
androgen levels normal T
and finally developed all the signs and symptoms of bronchogenic carcinoma

Bayliss[3] reported the case of a man, aged 56 years, who presented with acute "arthritis" associated with subperiosteal thickening of the bones of the limbs Six months later he developed gynæcomastia and cough A bronchogenic carcinoma was removed from the lower lobe of the right lung Within 24 hours of operation the osteoarthropathy had become quite painless, and within 48 hours the gynæcomastia
Liver function tests were
The patient was alive and
tion to this patient, Bayliss[4]
cinoma with gynæcomastia
and osteoarthropathy and four with gynæcomastia alone Sample and McCluskie[5] reported two cases of bronchogenic carcinoma, pulmonary osteoarthropathy and gynæcomastia and stated they had seen "several cases" of bronchogenic carcinoma and gynæcomastia

Fried[6] has suggested an endocrine basis for hypertrophic pulmonary osteoarthropathy, which he likens to certain features of acromegaly In a man who died of bronchogenic carcinoma complicated by osteoarthropathy and gynæcomastia, Fried found an increase in the size of the pituitary gland and the thyroid, together with multiple adenomata of the adrenal glands *Another patient with bronchogenic carcinoma and osteoarthropathy showed testicular atrophy without gynæcomastia.*

Among these eight published cases all showed osteoarthropathy and gynæcomastia, and their ages ranged from 41 to 63 years. The neoplasms have varied from operable peripheral growths to malignant hilar carcinomata with metastases.
of weight
r function
was seen
without osteoarthropathy

None of
ill endocrine studies, so
that the mecl
bronchogenic carcinoma
remains obscu
urinary œstrogens, but
details of the method of assay are not given, and some difficulties are encountered in the estimation and interpretation of urinary œstrogen levels, so that no great reliance can be placed upon this isolated observation. Furthermore, the source of
pulmonary
of growth
he gynæco-
stimulation
resulting from concomitant secretion of prolactin However, the reason for this over-activity of the pituitary gland remains unexplained, and this theory must be accepted with reservation The speed with which the two complications of arthropathy and gynæcomastia disappeared after operation in the patient reported by Bayliss directs attention to the tumour itself as a possible source of hormones or of some substance capable of stimulating breast tissue

A further bewildering observation has recently been reported in this connexion,

PULMONARY TUBERCULOSIS

Osler[10] is said to have taught that gynæcomastia sometimes appears early in the course of pulmonary tuberculosis, and since that time gynæcomastia has occasionally been reported in patients suffering from active pulmonary tuberculosis Wheeler *et alii*[7] recorded two cases, while Woodham[8] reported a case of pulmonary tuberculosis with testicular atrophy and gynæcomastia However, the occurrence of gynæcomastia in pulmonary tuberculosis is so rare that it would ordinarily pass as a coincidence One patient who showed such an association was seen at Guy's Hospital

Hormone Assays Estimation of 17-ketosteroid excretion gave the following results 7·1, 8 5, 5 2 and 9 0 mg per 24 hours Urinary gonadotrophin excretion was found to be $>32<72$;

>24<32 and >64<72 mouse units per 24 hours These results are within normal limits for a man of 70 years

Testicular Biopsy Biopsy (Figure 22) showed normal Leydig cells, and the tubular contents varied between normal spermatogenesis on the one hand and Sertoli cells only on the other hand Some tubules showed arrest of spermatogenesis at the stage of primary spermatocytes, but in most there was normal spermatogenesis, and in all the basement membrane was normal This biopsy result is regarded as normal for a man of 70 years.

Liver Function Tests The following findings were obtained, serum protein content, 6·8 gm per 100 ml, serum albumin content, 3·2 gm per 100 ml, serum globulin content, 3·6 gm per 100 ml, albumin/globulin ratio, 0 88, serum alkaline phosphatase content, 8·6 K A units per 100 ml, thymol turbidity, 10 units, thymol flocculation, +, colloidal gold reaction, + bromsulphalein test, 100% of the dye present after 5 minutes, 5% of the dye present after 45 minutes

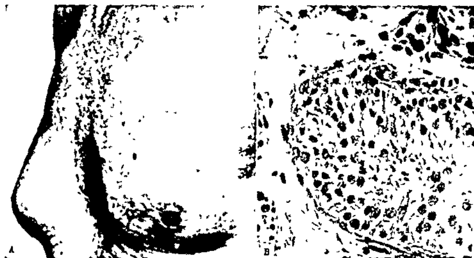


FIGURE 22

(A) Gynæcomastia in a patient suffering from pulmonary tuberculosis (B) Testicular biopsy from the same patient showing normal spermatogenesis and Leydig cells

One month later the following findings were obtained direct Van den Bergh reaction, negative, serum bilirubin content 0 05 mg per 100 ml, thymol turbidity, negative, thymol flocculation, negative, colloidal gold reaction, +, serum protein content, 6 9 gm per 100 ml, serum albumin content, 3 6 gm per 100 ml, serum globulin content, 3 3 gm per 100 ml, albumin/globulin ratio, 1 1

These investigations exclude liver failure as the cause of the gynæcomastia The thymol

increased the demand for vitamin B complex A basal metabolic rate determination was not possible, because the patient's sputum contained acid-fast bacilli

... was performed in order to exclude the possibility of a relative or
The result of the test (Table XXVIII) was almost within
eated three days after the completion of a course of intra-
ee page 95), 2 c c daily, for one week (second test) The
the gynæcomastia was unaffected by this treatment, so
be excluded as a cause of gynæcomastia in this patient

ætiological factor, no other cases have been reported in which this association was

mastia (see page 42)

TABLE XXVIII

Time	Blood Pyruvate Content (Mg 100 ml)		
	First Test	Second Test	Upper Limits of Normal
Fasting	1 29	1 24	1 1
60 minutes	1 38	1 32	1 38
90 minutes	1 12	1 11	1 38

BRONCHIECTASIS AND EMPYEMA

No good evidence has so far been reported to establish the occurrence of gynæcomastia associated with bronchiectasis or empyema as anything more than a coincidence

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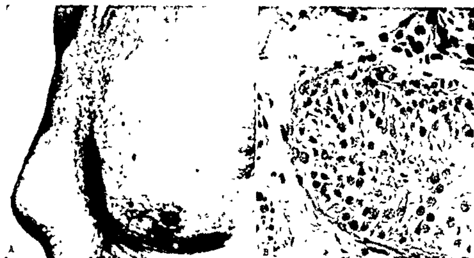


FIGURE 22

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After these investigations the patient was treated with streptomycin (one gramme daily) ... After four weeks the fever subsided, the sputum ... showed healing of cavities ... iastia persisted unchanged ... weeks

The endocrine component of this syndrome resembles Klinefelter's syndrome, i.e., small testes, absence of spermatogenesis, gynæcomastia and raised urinary gonadotrophin levels. However, the histological appearance of the testes was different from that of Klinefelter's syndrome. In these two patients the seminiferous

excretion
ed (>180
prostatic

The osseous lesions in these two patients included cubitus valgus, bilateral cervical ribs and a series of deformities of the cervical vertebræ—namely, reversal of the normal lordotic cervical curve due to atlanto-occipital fusion and partial fusion of the spinous processes and posterior articulations of the second and third cervical vertebræ, moderate hypertrophy of the bodies of the fifth, sixth and seventh cervical vertebræ and diminished intervertebral spaces.

The authors suggest that the occurrence of the syndrome in brothers, the association with other congenital deformities and the occurrence of mental deficiency in other members of the family all point to the congenital origin of the testicular

Roth[4] has reported a family of four brothers who suffered from hypogonadism

Reifenstein[5] has reported an interesting Syrian family, the male members of which were affected by Klinefelter's syndrome. Five brothers were all affected, and of the three sisters one was the mother of two sons, both of whom showed the syndrome, and the second had three sons, of whom two were affected. In each case the typical syndrome was present and gynæcomastia was marked. Klinefelter's syndrome is not usually hereditary, and it would be interesting to examine the chromosomal sex of the affected members of this family.

No reports have so far appeared to indicate that prepubertal testicular failure is hereditary.

THE INHERITANCE OF SUSCEPTIBLE MAMMARY TISSUE

When gynæcomastia appears as an isolated symptom, it is sometimes ignored and sometimes treated with secrecy, with the result that an hereditary or familial tendency is easily overlooked. The number of patients who indicate that other members of their families showed gynæcomastia must therefore be regarded as setting a minimum to the familial occurrence of this condition.

CHAPTER XV

GYNÆCOMASTIA AND HEREDITY

Since gynæcomastia is a symptom or sign which appears in association with a number of diseases, familial or hereditary tendencies would be expected to bear some relationship to the familial or hereditary occurrence of the causative conditions. It is therefore a mistake to speak of the inheritance of gynæcomastia without reference *to such causative conditions. It is not proposed to discuss the possible inheritance* of such causative factors as cirrhosis of the liver, bronchogenic carcinoma, thyrotoxicosis etc., but to confine the discussion to two problems, namely (i) the inheritance of those forms of male hypogonadism which are commonly associated with gynæcomastia, (ii) the possible inheritance of breast tissue which may be hypersensitive to hormonal influences

THE INHERITANCE OF HYPOGONADISM

In 1893 Savitsky[1] reported the occurrence of gynæcomastia associated with hypogonadism in a number of families. However, this aspect of the subject has been somewhat neglected until Peters and his co-workers[2] recently described the

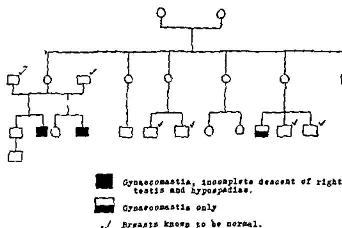


FIGURE 23

The occurrence of gynæcomastia in a family, including affected half-brothers whose fathers were unrelated

The case for maternal transmission of gynæcomastia in this family seems strong in view of the occurrence of the condition in half-brothers with unrelated fathers and the appearance of gynæcomastia in a maternal cousin (Figure 23)

Sohval and Soffer[3] have reported a syndrome in brothers which consists of mental deficiency, multiple congenital osseous anomalies, diabetes mellitus, some evidence of lack of androgen secretion, small testes, absence of spermatogenesis, gynæcomastia and raised urinary gonadotrophin levels Other members of the family were mentally deficient

The endocrine component of this syndrome resembles Klinefelter's syndrome, i e, small testes, absence of spermatogenesis, gynæcomastia and raised urinary gonadotrophin levels However, the histological appearance of the testes was different from that of Klinefelter's syndrome. In these two patients the seminiferous tubules were of two types The first were small, regular and close together, and did

of the changes in the basement membrane (see page 54). In addition, the Leydig

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and hereditary or familial

tend o indicate that other

members of their families showed gynæcomastia must therefore be regarded as setting a minimum to the familial occurrence of this condition.

One patient in the Guy's Hospital series and his brother both suffered from essential gynæcomastia at the age of 16 years and involutional gynæcomastia at the age of 52 years A sister showed unilateral breast development at the age of nine years—three years before the onset of other signs of puberty. It is not at present possible to account for these observations, but the isolated development of breast tissue without breast tissue in these patients Similar findings have been men which neonatal gynæcomastia 10 later showed essential gynæcomastia and in whom the essential gynæcomastia underwent spontaneous remission.

The inheritance of hypersensitive breast tissue, although of fundamental physiology of the breast, is too complex to be Much more information will be required before and it is to be hoped that future studies of accompanied by detailed enquiry concerning possible hereditary disturbances of breast function in members (of both sexes) of the patients' families

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CHAPTER XVI

THE MANAGEMENT AND TREATMENT OF GYNÆCOMASTIA

Since gynæcomastia is a symptom or sign, the treatment of this symptom is the treatment of the cause.

Neonatal gynæcomastia is common, and almost always subsides without treat-

puberty should be mentioned to the parents, who are to be encouraged to regard such a recurrence as a matter of no great importance and to expect spontaneous recovery

gynæcomastia

At puberty the most important step in the investigation of a patient with gynæcomastia is to exclude the common subareolar node, which is part of normal puberty This condition calls for no treatment, but it is important to reassure the patient and his parents and to point out that the condition invariably disappears without treatment Essential gynæcomastia is the next condition to be considered,

If puberty is
disease can be
be confirmed if
normal limits.

Essential gynæcomastia persists once it has developed and may cause serious embarrassment to the patient These are the considerations which determine the management of patients suffering from essential gynæcomastia, and the physician is faced with four alternatives—namely, no treatment, hormone therapy, radiotherapy and surgery

NO TREATMENT

to become very importunate in their demands for some form of treatment.

This point is illustrated by a medical student of 24 years who suffered gynæco-

The father jokingly dismissed the condition, but the patient insisted upon seeking another opinion and was eventually treated surgically with complete success It was to relieve such distress that 18 of 34 patients so affected were submitted to operation at Guy's Hospital

In general,
although such rem
For at least eight

constitute a period during which gynæcomastia is most distressing to the patient. It is possible that patients in whom the condition affects a brother, and has followed severe or protracted neonatal gynæcomastia, may show a spontaneous remission. In such patients a conservative policy is justified for two years. If no sign of remission has occurred during this time, surgery should be advised. The best way of assessing remission is by means of a photographic record.

not seem to regard the condition so seriously, and perhaps under these conditions watchful expectancy is justified. Parents may be more distressed than patients, although this is not easily detected with certainty during a single interview and in any case is probably an indication for surgical treatment.

HORMONE TREATMENT

The most extensive clinical and laboratory studies in these patients have not revealed any hormonal deficiency. In view of these negative findings and also the fact that androgenic hormones may not be without harm during puberty,[1] there can be no rational basis for the use of such preparations as testosterone in the treatment of essential gynæcomastia. This view is supported by the possibility that androgens may cause gynæcomastia under certain circumstances (page 125).

Moreover, the empirical use of androgens has shown them to be ineffective in ... ere given testosterone for ... ht by injection), and in no ... e is known at the present ... It is therefore concluded that hormone therapy has no place in the treatment of essential gynæcomastia.

RADIOTHERAPY

Deep X-ray therapy has been used in the treatment of gynæcomastia. Six ... orted to produce improve- ... ctive, and today clinicians ... patients where this can

SURGERY

Paulus Ægineta,[2] in the seventh century A.D., was the first to recommend the surgical treatment of gynæcomastia, and described a method for removing the breast through a semicircular incision, and in more extensive cases through two incisions. He advised operation upon the grounds that the condition "bears the reproach of effeminacy". Today the indication for operation is still the same, but the technique of Paulus Ægineta should no longer be used. This operation involves total mastectomy, and leaves a large scar, which constitutes as great a source of embarrassment as the gynæcomastia itself. Dartigues,[3] in 1928, described an operation which ...

gives good results and leaves a scar which is less conspicuous than that of the ... procedure.

... Webster[4, 5] has described the operation which has revolutionized the ...

skin nearly always leave inconspicuous ...

is that hæmostasis is difficult, and hæmatoma can occur, but this complication responds to simple measures. Commander George V. Webster, formerly resident

[illegible]

junction of the areola and the skin of the chest wall. This operation allows the entire breast to be removed and yet leaves a scar so fine that it has been known to escape [illegible] When such a [illegible] surgical [illegible] ent is at [illegible] ractical [illegible] waiting is rarely rewarded.

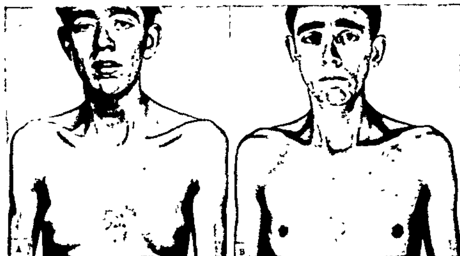


FIGURE 24
The Jerome Webster operation The patient is shown before and after operation, no scar is visible on casual inspection of the chest

At puberty, gynæcomastia due to prepubertal testicular failure and Klinefelter's syndrome may occur, and clinical examination of the testes will show that they are abnormal, while urinary gonadotrophins are raised by the time gynæcomastia develops Testicular biopsy and chromosomal sex determination will confirm the diagnosis. Here the treatment is that appropriate to the causative condition Prepubertal testicular failure should be treated by replacement doses of testosterone—implants of six pellets, each of 100 mg, will last up to six months This treatment promotes the development of secondary sexual characteristics, but of course does not affect the sterility, which is complete and permanent, nor the gynæcomastia, which, however, is not usually severe. Here the question of operation upon the breasts will be decided by the extent to which the patient complains of the gynæcomastia If this symptom appears to be distressing, operation can be advised Some explanation of the nature of the disease and the extent to which improvement can be expected is helpful, and some such patients have married successfully.

Klinefelter's syndrome presents a different problem The patient is to be treated as male, regardless of chromosomal sex, and neither he nor his relatives informed of the genetic sex in cases where this is female. Operative removal of breast tissue is

advisable, and testosterone has been administered as a means of encouraging the development of male secondary sexual characteristics. However, the sexual development of these patients is often adequate and not greatly improved by androgen therapy. If the secondary sexual characteristics are poorly developed and libido *and erections inadequate, testosterone* is to be recommended. These patients are, of course, permanently sterile, and should be informed of this. Gynæcomastia is not affected by testosterone in Klinefelter's syndrome, and the indication for surgery is the same as that in prepubertal testicular failure.

During adolescence and manhood *gynæcomastia associated with testicular* tumour may occur, and although this is rare, such an association is important, because gynæcomastia may be the first sign of a testicular tumour and in this way may offer the possibility of early treatment. At this time of life other testicular lesions may occur, such as testicular atrophy (unilateral or bilateral), undescended *testes, varicocele etc. Other* causes of gynæcomastia, such as leprosy, cirrhosis, bronchogenic carcinoma and thyrotoxicosis, occur during adult life, and in general

be considered

Adrenocortical disease is another uncommon cause of gynæcomastia in adult life, and for this reason estimation of urinary 17-ketosteroids and, where possible, *17-hydroxycorticosteroids and œstrogens, should form part of the laboratory* investigations of a case of gynæcomastia.

Drugs which cause gynæcomastia do not provide diagnostic problems if this possibility is kept in mind, but when gynæcomastia remains unexplained, contact with œstrogens should be considered—especial note of the patient's occupation being advisable.

...considerable care is

Observation

tainty. Most

al function are

nt if they are

ases). Some-

times the condition undergoes spontaneous remission, so that surgery is not as frequently indicated as in the case of essential gynæcomastia.

Sometimes the possibility of malignant changes supervening in cases of established gynæcomastia has been proposed as a reason for early and radical removal of the breasts in all cases of gynæcomastia. That this argument is without foundation is shown by the observation that among more than 700 recorded cases of gynæcomastia *only two have been reported as the site of malignant disease.* Berns[7] reported a carcinoma occurring in a case of gynæcomastia which eventually led to death. Edheim[8] described a malignant duct papilloma in a case of gynæcomastia, but the diagnosis of malignancy was purely histological. These observations indicate that the possibility of malignant change should not influence the routine treatment of gynæcomastia, *but if a hard lump develops in an established case of gynæcomastia,* biopsy is indicated. It should be remembered that axillary glands not infrequently become enlarged during the early stages of gynæcomastia, especially when the breasts are tender, but this does not of course indicate the presence of malignant disease.

In men receiving œstrogen therapy for carcinoma of the prostate, it is important to bear in mind the possibility of *malignant change in the enlarged breasts. It is* likely that most carcinomata reported in such patients are due to metastases from the primary growth and should not be regarded as a contraindication for œstrogen therapy in carcinoma of the prostate.[12] Either as the result of longer survival or

because of changes in the stimulated breasts which encourage metastatic deposits to grow, secondary carcinoma has been reported in a number of cases of prostatic carcinoma receiving œstrogens Considerable care is needed to demonstrate the nature of these tumours and enzyme studies may be required to prove that the lesion in the breast is not a primary carcinoma

It was pointed out in Chapter IX that gynæcomastia may be associated with transvestism While the definitive treatment of this condition has yet to be established, it seems unwise at present to undertake measures designed to turn these

only to express deep regret at having submitted to this procedure—perhaps the photographer has captured this regret in Figure 24 Hamburger[9, 10] also mentions a patient who expressed similar feelings after such an operation.

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SUMMARY AND CONCLUSIONS

Gynæcomastia may be defined as enlargement of the glandular component of the breast in males This definition is useful to the clinician and the pathologist alike, being free of contention

Gynæcomastia has been known since the days of ancient Greek medicine, but

of the normal male breast after stimulation by œstrogens

Gynæcomastia may be associated with physiological life epochs, and of these there are three—namely bi

puberty, which may be as

which may be associated

is distinguished from the

normal puberty, by its severity and its persistence

Prepubertal testicular failure is frequently complicated by the presence of gynæcomastia, although the degree of breast development is usually slight and of *little consequence beside the failure of sexual development. On the other hand,* surgical castration before or after puberty seldom, if ever, causes gynæcomastia

Tumours of the testis (chorionepithelioma, seminoma, interstitial cell tumour and Sertoli cell tumour) occasionally cause gynæcomastia, probably due to the secretion of œstrogens by the tumour cells, except in the case of chorionepithelioma,

orchitis of unknown ætiology which leads to testicular atrophy.

Klinefelter's syndrome consists of small testes, azoospermia, raised levels of

relationship be

stimulation of

would not the

cells could do the same, either by producing excessive quantities of androgens or of œstrogens

A histological picture resembling that of Klinefelter's syndrome is found in a number of diseases, and some of these are associated with gynæcomastia—e g ,

dystrophia myotonica,

maphroditism

] with gynæco-mastia, which then becomes a sign of great diagnostic importance For this reason urinary 17-ketosteroid and œstrogen excretion should be measured in any case of unexplained gynæcomastia in an adult Liver cell failure may be associated with gynæcomastia, which is possibly due to failure of the liver cells to conjugate the œstrogens normally produced by the testis and possibly by the adrenal cortex Cirrhosis is the most important form of liver disease to cause gynæcomastia, but advanced failure of liver cells due to any cause may produce gynæcomastia.

Hæmochromatosis is probably the one exception to the last statement, and it is likely that deposits of hæmosiderin interfere with the function of the adenohypophysis, which in turn deprives the testis of its usual gonadotrophic stimulation; in the absence of adequate gonadotrophic activity, breast stimulation does not occur.

reaw
state
flush of puberty.

Among the drugs which can
potent. Prolonged administration
and it is possible that conversion of
responsible for this occurrence In exceptional cases, adrenocortical hormones,

Bronchogenic carcinoma has been known to cause gynæcomastia, but the mechanism is quite obscure Pulmonary tuberculosis is rarely associated with gynæcomastia

Breast tissue shows considerable variation in its susceptibility to hormonal influences The age at which exposure to such influences first occurs is probably significant, and in addition there is considerable variation from one individual to another in the response to a given stimulus Even in one person the two breasts may develop asymmetrically, this difference is seen in its most extreme form in lateral hermaphroditism, in which a normal female breast develops on one side of the body in the absence of any breast development on the other side No doubt there are local factors inherent in mammary tissue which determine these differences Moreover, there is considerable variation in the duration of a given response following a given stimulus Sometimes a period of breast stimulation is followed by more or less permanent gynæcomastia, which persists long after the stimulating influence has been withdrawn, at other times the breast resumes its original state after the stimulating influence has been removed It is possible that some of these variations in the behaviour of breast tissue are genetic in origin

Not infrequently gynæcomastia appears in patients suffering from an underlying disease not usually regarded as a cause of this symptom Such associations are for the most part fortuitous, or the underlying disease has precipitated the gynæcomastia as the result of some non-specific mechanism which cannot at present be explained

The trea f the cause Those patients who find esse sment should be advised to submit to the Under other circumstances the treatment of gynæcomastia is conservative

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